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(54) Title: NEW HETEROCYCLIC AMIDE COMPOUNDS USEFUL FOR THE TREATMENT OF INFLAMMATORY AND ALLERGIC DISORDERS: PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract: The present invention relates to novel heterocyclic compounds that inhibit phosphodiesterase type 4 (PDE 4). The compounds are useful for treating inflammatory conditions, diseases of the central nervous systems and insulin resistant diabetes.



**WO 2004/022536 A1**

NEW HETEROCYCLIC AMIDE COMPOUNDS USEFUL FOR  
THE TREATMENT OF INFLAMMATORY AND ALLERGIC  
DISORDERS: PROCESS FOR THEIR PREPARATION AND  
5 PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

**Field of the Invention**

The present invention relates to novel heterocyclic compounds. More particularly the present invention relates to novel phosphodiesterase type 4  
10 (PDE4) inhibitors having a heterocyclic structure, pharmaceutical compositions including such compounds, methods for their preparation and method for their use.

**Background of the Invention**

15 Airway inflammation characterizes a number of severe lung diseases including asthma and chronic obstructive pulmonary disease (COPD). Events leading to airway obstruction include edema of airway walls, infiltration of inflammatory cells into the lung, production of various inflammatory mediators and increased mucous production. The airways of asthmatic patients are infiltrated  
20 by inflammatory leukocytes, of which the eosinophil is the most prominent component. The magnitude of asthmatic reactions is correlated with the number of eosinophils present in lungs.

The accumulation of eosinophils is found dramatically in the lungs of asthmatic patients although there are very few in the lungs of a normal individual.  
25 They are capable of lysing and activating cells and destroying tissues. When activated, they synthesize and release inflammatory cytokines such as IL-1, IL-3, TNF- $\alpha$  and inflammatory mediators such as PAF, LTD4 and relative oxygen species that can produce edema, broncho-constriction. Tumor necrosis factor (TNF- $\alpha$ ) was also known to be involved in the pathogenesis of a number of  
30 autoimmune and inflammatory diseases. Consequently, manipulation of the cytokine signaling or biosynthetic pathways associated with these proteins may provide therapeutic benefit in those disease states. It has been well demonstrated

that TNF- $\alpha$  production in pro-inflammatory cells becomes attenuated by an elevation of intracellular cyclic adenosine 3',5'-monophosphate (cAMP). This second messenger is regulated by the phosphodiesterase (PDE) family of enzymes. The phosphodiesterase enzymes play an integral role in cell signaling mechanisms by hydrolyzing cAMP and cGP to their inactive 5' forms. Inhibition of PDE enzymes thus results in an elevation of cAMP and /or cGP levels and alters intracellular responses to extra cellular signals by affecting the processes mediated by cyclic nucleotides. Since eosinophils are believed to be a critical proinflammatory target for asthma, identification of the expression of PDE 4 gene family in eosinophils led to the PDE 4 as potential therapeutic target for asthma [Rogers, D.F., Giembycz, M.A., *Trends Pharmacol. Sci.*, 19, 160-164(1998); Barnes, P.J., *Trends Pharmacol. Sci.*, 19, 415-423 (1998) herein incorporated by reference in their entirety].

The mammalian cyclic nucleotide phosphodiesterases (PDEs) are classified into ten families on the basis of their amino acid sequences and/or DNA sequence, substrate specificity and sensitivity to pharmacological agents [Soderling, S.H., Bayuga, S.J., and Beavo, J.A., *Proc. Natl. Acad. Sci., USA*, 96,7071-7076 (1999); Fujishige, K, Kotera, J., Michibata, H., Yuasa, K., Takebayashi, Si, Okamura, K. and Omori, K., *J. Biol. Chem.*, 274, 18438-18445 (1999) herein incorporated by reference in their entirety]. Many cell types express more than one PDE and distribution of isoenzymes between the cells varies markedly. Therefore development of highly isoenzyme selective PDE inhibitors provides a unique opportunity for selective manipulation of various pathophysiological processes.

Phosphodiesterase type 4 (PDE4) is an enzyme which regulates activities in cells which lead to inflammation in the lungs. PDE4, a cAMP-specific and Ca<sup>+2</sup>-independent enzyme, is a key isozyme in the hydrolysis of cAMP in mast cells, basophils, eosinophils, monocytes and lymphocytes. The association between cAMP elevation in inflammatory cells with airway smooth muscle relaxation and inhibition of mediator release has led to widespread interest in the design of PDE4 inhibitors[Trophy,T.J., *Am. J. Respir. Crit. Care Med.*, 157, 351-370 (1998) herein incorporated by reference in its entirety]. Excessive or unregulated TNF- $\alpha$  production has been implicated in mediating or exacerbating a

number of undesirable physiological conditions such as diseases including osteoarthritis, and other arthritic conditions; septic shock, ecdotoxic shock, respiratory distress syndrome, bone resorption diseases ; Since TNF- $\alpha$  also participates in the onset and progress of autoimmune diseases, PDE4 inhibitors  
5 may find utility as therapeutic agents for rheumatoid arthritis, multiple sclerosis and Crohn's disease. [*Nature Medicine*, 1, 211-214 (1995) and *ibid.* 244-248 herein incorporated by reference in their entirety].

Strong interest in drugs capable of selective inhibition of PDE 4 is due to several factors such as (a) the tissue distribution of PDE-4 suggests that  
10 pathologies related to the central nervous and immune systems could be treated with selective PDE-4 inhibitors (b) the increase in intracellular cAMP concentration, the obvious biochemical consequence of PDE-4 inhibition, has been well characterized in immuno-competent cells where it acts as a deactivating signal.

15 Recently the PDE4 family has grown to include four subtypes-PDE4A to PDE4D each encoded by a distinct gene. (*British Journal of Pharmacology*; 1999; v.128; p.1393-1398) incorporated herein by reference in its entirety.

It has been demonstrated that increasing cAMP levels within these cells results in suppression of cell activation which in turn inhibits the production and  
20 release of pro-inflammatory cytokines such as TNF- $\alpha$ . Since eosinophils are believed to be a critical pro-inflammatory target for asthma, identification of the expression of the PDE-4 gene family in eosinophils led to the PDE-4 as potential therapeutic target for asthma.

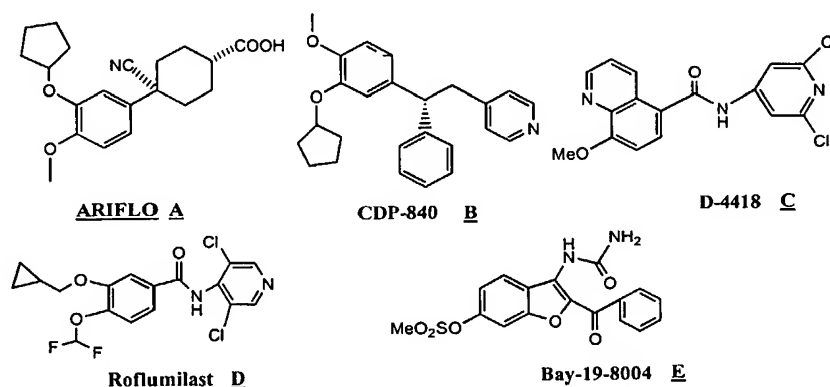
The usefulness of several PDE-4 inhibitors, unfortunately, is limited due to  
25 their undesirable side effect profile which include nausea and emesis (due to action on PDE-4 in the central nervous system) and gastric acid secretion due to action on PDE-4 in parietal cells in the gut. Barnette, M.S., Grous, M., Cieslinsky, L.B., Burman, M., Christensen, S.B., Trophy, T. J., *J. Pharmacol. Exp. Ther.*, 273, 1396-1402 (1995) herein incorporated by reference in their entirety.  
30 One of the earliest PDE-4 inhibitor, Rolipram, was withdrawn from the clinical development because of its severe unacceptable side effect profile. Zeller E. et. al., *Pharmacopsychiatr.*, 17, 188-190 (1984) herein incorporated by reference in



their entirety. The cause of severe side effects of several PDE-4 inhibitor molecules in human clinical trials has recently become apparent.

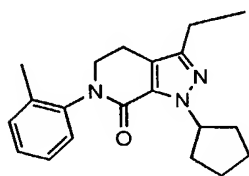
There exist two binding sites on mammalian PDE-4 at which inhibitor molecules may bind. Also PDE-4 exists in two distinct forms which represent different conformations. They are designated as High affinity Rolipram binding site PDE-4H and Low affinity Rolipram binding site PDE-4L [Jacobitz, S., McLaughlin, M.M., Livi, G.P., Burman, M., Trophy, T.J., *Mol. Pharmacol.*, **50**, 891-899 (1996) herein incorporated by reference in its entirety]. It was shown that certain side effects (vomiting and gastric acid secretion) are associated with inhibition of PDE-4H whereas some beneficial actions are associated with PDE-4L inhibition. It was also found that human recombinant PDE-4 exists in 4 isoforms A, B, C and D [Muller, T., Engels, P., Fozard, J.R., *Trends Pharmacol. Sci.*, **17**, 294-298 (1996) herein incorporated by reference in its entirety]. Accordingly, compounds displaying more PDE-4D isoenzyme selectivity over the A, B or C are found to have less amount of side effects than Rolipram [Hughes, B et al., *Br. J. Pharmacol.* **1996**, **118**, 1183-1191 herein incorporated by reference in its entirety]. Therefore, selective inhibitors of PDE-4 isozymes would have therapeutic effects in inflammatory diseases such as asthma and other respiratory diseases.

Although several research groups all over the world are working to find highly selective PDE-4 isozyme inhibitors, so far success is limited. Various compounds have shown PDE-4 inhibition.

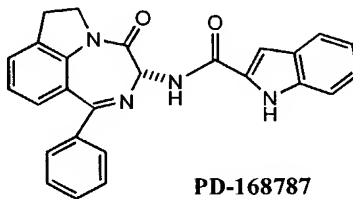


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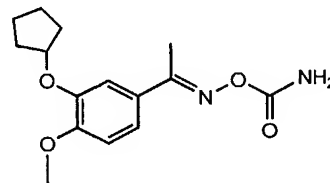
SmithKline Beecham's "Ariflo" which has the formula A, Byk Gulden's Roflumilast which has the formula D and Bayer's Bay-19-8004 which has the  
 5 formula E have reached advanced stage of human clinical trials. Other compounds which have shown potent PDE-4 inhibitory activity include Celltech's CDP-840 of the formula B, Schering Plough's D-4418 of the formula C, Pfizer's 5CP-220,629 which has the formula F, Parke Davis's PD-168787 which has the



CP - 220,629



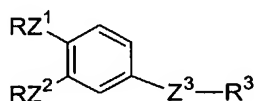
PD-168787



Filaminast

formula G and Wyeth's Filaminast which has the formula H. However, recently  
 10 due to efficacy and side effects problems, Ariflo, CDP-840 and Bay-19-8004 were discontinued from clinical trials as a treatment for asthma. Other compounds of the formula C and F are presently undergoing phase-1 clinical trials.

PCT publication WO95/04046, incorporated herein by reference in its entirety, is directed to a compound of formula 1, said to be useful for inhibiting  
 15 the production or physiological effects of TNF in the treatment of a patient suffering from a disease state associated with a physiologically detrimental excess of tumor necrosis factor (TNF), where formula I is as follows:

**1**

20 wherein

R<sup>1</sup> is lower alkyl;

R<sup>2</sup> is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cyclothioalkyl or cyclothioalkenyl;

R<sup>3</sup> is aryl or heteroaryl;

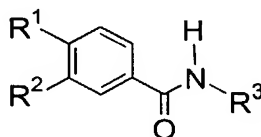
25 Z<sup>1</sup> and Z<sup>2</sup> are independently oxygen, sulfur or direct bond, and only one of Z<sup>1</sup> and Z<sup>2</sup> is a direct bond;

Z<sup>3</sup> is -CZCH<sub>2</sub>- or -CZNH- ; and

Z is oxygen or sulfur,  
or N-oxide thereof or a pharmaceutically accepted salts thereof,  
provided that

- when Z<sup>2</sup> is a direct bond, R<sup>2</sup> is alkyl bonded to the phenyl moiety via a  
5 nonquaternary carbon, alkenyl, alkynyl, cyclothioalkyl or cyclothioalkenyl, or R<sup>3</sup> is  
azaheteroaryl having a nitrogen atom thereof oxidized to the corresponding N-  
oxide moiety.

- 2) US granted patent US 5,712,298 issued on January 27, 1998 and  
10 issued to BYK Gulden Lomberg Chemische Fabrik GMBH, incorporated herein  
by reference in its entirety, is directed to compounds of the formula 2



- 15 (2)

wherein

- one of the substituents R1 and R2 is hydrogen, 1-6C-alkoxy, 3-7C- cycloalkoxy,  
3-7C cycloalkylmethoxy, benzyloxy or 1-4C-alkoxy which is completely or  
20 partially substituted by fluorine, and other 1-4C- which is completely or partially  
substituted by fluorine, and

R3 is phenyl, pyridyl, phenyl which is substituted by R31, R32 and R33 or pyridyl  
which is substituted by R34, R35, R36 and R37, where

- R31 is hydroxyl, hydrogen, cyano, carboxyl, trifluoromethyl, 1-4C-alkyl, 1-4C-  
25 alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonyloxy, amino,  
mono- or di-1-4C-alkylamino or 1-4C-alkylcarbonylamino,

R32 is hydrogen, hydroxyl, halogen, amino, trifluoromethyl, 1-4C-alkyl or 1-4C-  
alkoxy,

R33 is hydrogen, hydroxyl, halogen, 1-4C-alkyl or 1-4C-alkoxy,

- 30 R34 is hydrogen; halogen, cyano, carboxyl, alkyl, 1-4C-alkoxy, 1-4C-  
alkoxycarbonyl or amino,

R35 is hydrogen, halogen, amino, 1-4C-alkyl,

R36 is hydrogen or halogen and

R<sup>37</sup> is hydrogen or halogen,

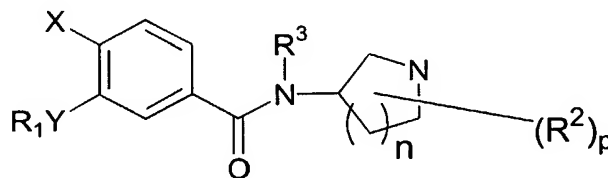
the salts of these compounds, and the N-oxides of the pyridines and their salts.

Accordingly we have prepared a novel series of compounds having the general formula **I** as defined below. We have examined the *in vitro* efficacy of these novel compounds against human PDE-4 enzyme and they have been found to show excellent PDE-4 enzyme inhibition activity at nM-μM concentrations. The compounds of the present invention are useful as therapeutic agents for inflammatory allergic diseases particularly bronchial asthma, allergic rhinitis and nephritis. Since these compounds also inhibit the production of tumor necrosis factor (TNF), they may also find use in autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, Crohn's disease, psoriasis ; diseases of the central nervous system such as depression amnesia, and dementia, cardiac failure, shock, and cerebrovascular disease and the like ; insulin-resistant diabetes.

15

### SUMMARY OF THE INVENTION

Accordingly, the present invention provides novel heterocyclic compounds of the general formula (**I**),



20

(**I**)

wherein,

R<sup>1</sup> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl, -C(O)-R<sup>1</sup>, -C(O)O-R<sup>1</sup>, -C(O)NR<sup>1</sup>R<sup>1</sup> or -S(O)<sub>m</sub>-R<sup>1</sup>; preferably R<sup>1</sup> is substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl

wherein Y represents direct bond, oxygen, sulfur or  $\text{NR}^1$ ; preferably Y is oxygen  
wherein X is a hydrogen, halogen atom,  $-\text{OR}^1$ ,  $-\text{S}(\text{O})_m \text{R}^1$ ,  $-\text{C}(\text{O})\text{R}^1$ , formyl  
amine, nitro or  $-\text{NR}^x\text{R}^y$  (wherein  $\text{R}^x$  and  $\text{R}^y$  independently represents hydrogen  
atom, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted  
5 arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl,  
substituted or unsubstituted cycloalkenyl substituted or unsubstituted heterocyclic  
ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
heteroaryl or substituted or unsubstituted heteroarylalkyl ); preferably X is  
substituted or unsubstituted alkoxy

10 wherein m is 0, 1 or 2;

wherein  $\text{R}^2$  is hydrogen, substituted or unsubstituted alkyl, substituted or  
unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or  
unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or  
unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl,  
15 substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl,  
substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic  
group, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
heteroarylalkyl, oxo ( $=\text{O}$ ), thio ( $=\text{S}$ ), hydroxy, amino, cyano, nitro, halogen,  
carboxyl, formyl; preferably  $\text{R}^2$  is hydrogen, substituted or unsubstituted alkyl,  
20 substituted or unsubstituted aryl, substituted or unsubstituted aryl alkyl,  
substituted or unsubstituted cycloalkyl, substituted or unsubstituted  
cycloalkylalkyl, or oxo( $=\text{O}$ );

wherein  $\text{R}^3$  represents hydrogen, substituted or unsubstituted alkyl, substituted or  
25 unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or  
unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or  
unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl,  
substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl,  
substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic  
30 group, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
heteroarylalkyl or hydroxy; preferably  $\text{R}^3$  is hydrogen;

wherein n = 1 or 2;

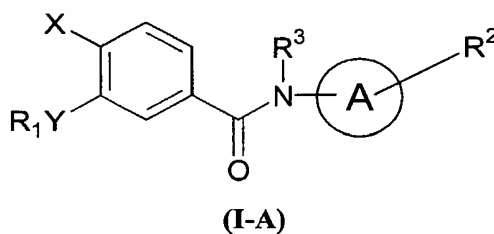
wherein p = 1, 2, 3, 4 or 5; with the proviso that

if  $n = 1$  then  $p = 1, 2, 3$  or  $4$ , and

if  $n = 2$  then  $p = 1, 2, 3, 4$  or  $5$

and their analogs, their tautomers, their regioisomers, their diastereomers, their stereoisomers, their geometrical isomers, their N-oxides, their polymorphs, their pharmaceutically acceptable salts, and their pharmaceutically acceptable solvates thereof.

In another aspect of the present invention there is provided a compound of general formula (I-A)



wherein,

$R^1$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl,  $-C(O)-R^1$ ,  $-C(O)O-R^1$ ,  $-C(O)NR^1R^1$  or  $-S(O)_m-R^1$ ; preferably  $R^1$  is substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl

wherein Y represents direct bond, oxygen, sulfur or  $NR^1$ ; preferably Y is oxygen

wherein X is a hydrogen, halogen atom,  $-OR^1$ ,  $-S(O)_m R^1$ ,  $-C(O)R^1$ , formyl amine, nitro or  $-NR^xR^y$  (wherein  $R^x$  and  $R^y$  independently represents hydrogen atom, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted

heteroaryl or substituted or unsubstituted heteroarylalkyl ); preferably X is substituted or unsubstituted alkoxy

wherein m is 0, 1 or 2;

wherein R<sup>2</sup> is hydrogen, substituted or unsubstituted alkyl, substituted or  
5 unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or  
unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or  
unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl,  
substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl,  
substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic  
10 group, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
heteroarylalkyl, oxo (=O), thio (=S), hydroxy, amino, cyano, nitro, halogen,  
carboxyl, formyl; preferably R<sup>2</sup> is hydrogen, substituted or unsubstituted alkyl,  
substituted or unsubstituted aryl, substituted or unsubstituted aryl alkyl,  
substituted or unsubstituted cycloalkyl, substituted or unsubstituted  
15 cycloalkylalkyl, or oxo(=O);

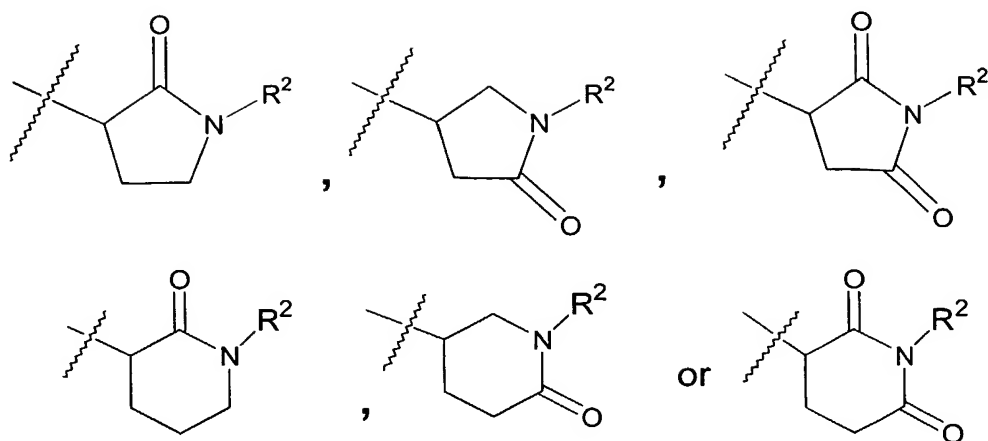
wherein R<sup>3</sup> represents hydrogen, substituted or unsubstituted alkyl, substituted or  
unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or  
unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or  
20 unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl,  
substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl,  
substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic  
group, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
heteroarylalkyl or hydroxy; preferably R<sup>3</sup> is hydrogen;

25 wherein p = 1, 2 or 3 ;

the A ring represents a heterocyclic ring

wherein R<sup>2</sup> is chosen independently for each position capable of substitution,  
the preferable ring A can be selected from

30



and their analogs, their tautomers, their regioisomers, their diastereomers, their stereoisomers, their geometrical isomers, their N-oxides, their polymorphs, their  
5 pharmaceutically acceptable salts, and their pharmaceutically acceptable solvates thereof.



**DETAILED DESCRIPTION OF THE INVENTION**

The term 'alkyl' refers to a straight or branched hydrocarbon chain radical having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, examples include but are not limited to methyl, ethyl, 5 n-propyl, and 1-methylethyl (isopropyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl).

The term "alkenyl" refers to aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched chain radical having 2 to 10 carbon atoms which is attached to the rest of the molecule by a 10 single bond. Examples include but are not limited to ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl and the like.

The term "alkynyl" refers to straight or branched chain hydrocarbon radicals having at least one carbon-carbon triple bond, having 2 to 12 carbon 15 atoms (with radicals having in the range of about 2 up to 10 carbon atoms preferred) which is attached to the rest of the molecule by a single bond. Examples include but is not limited to ethynyl, propynyl, and butynyl.

The term "alkoxy" denotes alkyl group as defined above attached via oxygen linkage to the rest of the molecule. Examples include but are not limited 20 to  $-\text{OCH}_3$ , -and  $-\text{OC}_2\text{H}_5$ .

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of 3 to about 14 carbon atoms attached via a single bond to the rest of the molecule. Examples of monocyclic ring system include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl and, cyclohexyl. Examples of multicyclic 25 ring system include but are not limited to perhydronaphthyl, adamantyl and norbornyl groups bridged cyclic group or spirobicyclic groups e.g. spiro (4,4) non-2-yl.

The term "cycloalkylalkyl" refers to cyclic ring-containing radical containing 3 to about 8 carbon atoms directly attached to alkyl group which is 30 then attached to the main structure at any carbon from alkyl group that results in the creation of a stable structure. such as cyclopropylmethyl, cyclobutylethyl, cyclopentylethyl, and the like.

The term “cycloalkenyl” refers to cyclic ring-containing radicals containing in the range of about 3 up to 8 carbon atoms with at least one carbon-carbon double bond. Examples include but are not limited to cyclopropenyl, cyclobutenyl and cyclopentenyl.

5       The term “aryl” refers to aromatic radicals having 6 to 14 carbon atoms. Examples include but are not limited to phenyl, naphthyl, tetrahydronaphthyl, indanyl and biphenyl.

The term “arylalkyl” refers to an aryl ring as defined above directly bonded to an alkyl group as defined above. Examples include but are not limited

10 to  $-\text{CH}_2\text{C}_6\text{H}_5$ , and  $-\text{C}_2\text{H}_5\text{C}_6\text{H}_5$ .

The term "heterocyclic ring" refers to a stable 3- to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. For purpose of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the heterocyclic ring radical may be partially or fully saturated or aromatic (heteroaromatic). Examples of such heterocyclic ring radicals include, but are not limited to, azetidiny, acridiny, benzodioxoly, benzodioxany, benzofurnyl, carbazoly, cinnolinyl, dioxolany, indoliziny, naphthyridiny, perhydroazepiny, phenaziny, phenothiaziny, phenoxaziny, phthalaziny, pyridyl pteridiny, puriny, quinazolinyl, quinoxaliny, quinolinyl, isoquinolinyl, tetrazoly, imidazoly, tetrahydroisoquinoly, piperidiny, piperaziny, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidiny, 2-oxoazepiny, azepiny, pyrroly, 4-piperidony, pyrrolidiny, pyraziny, pyrimidiny, pyridaziny, oxazoly, oxazolinyl, oxasolidiny, triazoly, indany, isoxazoly, isoxasolidiny, morpholinyl, thiazoly, thiazolinyl, thiazolidiny, isothiazoly, quinuclidiny, isothiazolidiny, indoly, isoindoly, indolinyl, isoindolinyl, octahydroindoly, octahydroisoindoly, quinoly, isoquinoly, decahydroisoquinoly, benzimidazoly, thiadiazoly, benzopyrany, benzothiazoly, benzooxazoly, furyl, tetrahydrofuryl, tetrahydropyrany, thienyl,

benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide thiamorpholinyl sulfone, dioxaphospholanyl, oxadiazolyl, chromanyl and isochromanyl.

The term "heteroarylalkyl" refers to heteroaryl ring radical as defined above directly bonded to alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom from alkyl group that results in the creation of a stable structure.

The term "heterocyclalkyl" refers to a heterocyclic ring radical as defined above directly bonded to alkyl group. The heterocyclalkyl radical may be attached to the main structure at carbon atom in the alkyl group that results in the creation of a stable structure.

The term "halogen" refers to radicals of fluorine, chlorine, bromine, iodine.

The substituents in the 'substituted alkyl', 'substituted alkoxy' 'substituted alkenyl' 'substituted alkynyl' 'substituted cycloalkyl' substituted cycloalkylalkyl' substituted cycloalkenyl' 'substituted arylalkyl' 'substituted aryl' 'substituted heterocyclic ring', 'substituted heteroaryl ring,' 'substituted heteroarylalkyl', 'substituted heterocyclalkyl ring', 'substituted amino', 'substituted alkoxy carbonyl', 'substituted cyclic ring' 'substituted alkyl carbonyl', 'substituted alkyl carbonyloxy' and 'substituted carboxylic acid' may be the same or different which one or more selected from the groups such as hydrogen, hydroxy, halogen, carboxyl, cyano, amino, nitro, oxo (=O), thio (=S), or optionally substituted groups selected from alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, aryl, heteroaryl, heteroarylalkyl, heterocyclic ring, -COOR<sup>x</sup>, -C(O)R<sup>x</sup>, -C(S)R<sup>x</sup>, -C(O)NR<sup>x</sup>R<sup>y</sup>, -C(O)ONR<sup>x</sup>R<sup>y</sup>, -NR<sup>x</sup>CONR<sup>y</sup>R<sup>z</sup>, -N(R<sup>x</sup>)SOR<sup>y</sup>, -N(R<sup>x</sup>)SO<sub>2</sub>R<sup>y</sup>, -(=N-N(R<sup>x</sup>)R<sup>y</sup>), -NR<sup>x</sup>C(O)OR<sup>y</sup>, -NR<sup>x</sup>R<sup>y</sup>, -NR<sup>x</sup>C(O)R<sup>y</sup>, -NR<sup>x</sup>C(S)R<sup>y</sup>, -NR<sup>x</sup>C(S)NR<sup>y</sup>R<sup>z</sup>, -SONR<sup>x</sup>R<sup>y</sup>, -SO<sub>2</sub>NR<sup>x</sup>R<sup>y</sup>, -OR<sup>x</sup>, -OR<sup>x</sup>C(O)NR<sup>y</sup>R<sup>z</sup>, -OR<sup>x</sup>C(O)OR<sup>y</sup>, -OC(O)R<sup>x</sup>, -OC(O)NR<sup>x</sup>R<sup>y</sup>, -R<sup>x</sup>NR<sup>y</sup>R<sup>z</sup>, -R<sup>x</sup>R<sup>y</sup>R<sup>z</sup>, -R<sup>x</sup>CF<sub>3</sub>, -R<sup>x</sup>NR<sup>y</sup>C(O)R<sup>z</sup>, -R<sup>x</sup>OR<sup>y</sup>, -R<sup>x</sup>C(O)OR<sup>y</sup>, -R<sup>x</sup>C(O)NR<sup>y</sup>R<sup>z</sup>, -R<sup>x</sup>C(O)R<sup>x</sup>, -R<sup>x</sup>OC(O)R<sup>y</sup>, -SR<sup>x</sup>, -SOR<sup>x</sup>, -SO<sub>2</sub>R<sup>x</sup>, -ONO<sub>2</sub>, (wherein R<sup>x</sup>, R<sup>y</sup> and R<sup>z</sup> in each of the above groups can be hydrogen atom, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl substituted

or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heteroarylalkyl.

Pharmaceutically acceptable salts forming part of this invention include

5 salts derived from inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Zn, Mn; salts of organic bases such as N,N'-diacetylenediamine, glucamine, triethylamine, choline, choline hydroxide, dicyclohexylamine, metformin, benzylamine, trialkylamine, thiamine, spermidine, and the like; chiral bases like alkylphenylamine, glycinol, phenyl glycinol and the like, salts of natural amino

10 acids such as glycine, alanine, valine, leucine, isoleucine, norleucine, tyrosine, cystine, cysteine, methionine, proline, hydroxy proline, histidine, ornithine, lysine, arginine, serine, and the like; unnatural amino acids such as D-isomers or substituted amino acids; guanidine, substituted guanidine wherein the substituents are selected from nitro, amino, alkyl, alkenyl, alkynyl, ammonium or substituted

15 ammonium salts and aluminum salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, benzoates, salicylates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable

20 solvates may be hydrates or comprise other solvents of crystallization such as alcohols.

Another object of the invention is a method of treating inflammatory diseases, disorders and conditions characterized by or associated with an undesirable inflammatory immune response and all disease and conditions

25 induced by or associated with an excessive secretion of TNF- $\alpha$  and PDE-4 which comprises administering to a subject a therapeutically effective amount of a compound according to Formula Ia.

Another object of the invention is a method of treating inflammatory conditions and immune disorders in a subject in need thereof which comprises

30 administering to said subject a therapeutically effective amount of a compound according to Formula Ia.

Preferred inflammatory conditions and immune disorders are chosen from the group consisting of: asthma, bronchial asthma, chronic obstructive pulmonary disease, allergic rhinitis, eosinophilic granuloma, nephritis, rheumatoid arthritis,

cystic fibrosis, chronic bronchitis, multiple sclerosis, Crohns disease, psoriasis, uticaria, adult vernal conjunctivitis, respiratory distress syndrome, rheumatoid spondylitis, osteoarthritis, gouty arthritis, utelitis, allergic conjunctivitis, inflammatory bowel conditions, ulcerative coalitis, eczema, atopic dermatitis and  
5 chronic inflammation.

Further preferred is when the inflammatory condition is an allergic inflammatory condition.

Further preferred is when the inflammatory conditions and immune disorders are selected from the group consisting of inflammatory conditions or  
10 immune disorders of the lungs, joints, eyes, bowels, skin and heart.

Further preferred is when the inflammatory condition is chosen from the group consisting of: bronchial asthma, nepritis, and allergic rhinitis.

Another object of the invention is a method for abating inflammation in an affected organ or tissue comprising delivering to said organ or tissue a  
15 therapeutically effective amount of a compound represented by a compound according to Formula 1a.

Another object of the invention is a method of treating diseases of the central nervous system in a subject in need thereof which comprises administering to said subject a therapeutically effective amount of a compound according to  
20 Formula 1a.

Preferred diseases of the central nervous system are chosen from the group consisting of: depression, amnesia, dementia, Alzheimers disease, cardiac failure, shock and cerebrovascular disease.

Another object of the invention is a method of treating insulin resistant  
25 diabetes in a subject in need thereof which comprises administering to said subject a therapeutically effective amount of a compound according to formula 1.

"Treating" or "treatment" of a state, disorder or condition includes:

(1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a mammal that may be afflicted with or  
30 predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition,

(2) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof,  
or

(3) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician

5       A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the mammal to be treated.

10       The four classic symptoms of acute inflammation are redness, elevated temperature. Swelling, and pain in the affected area, and loss of function of the affected organ.

Symptoms and signs of inflammation associated with specific conditions include:

- 15       • rheumatoid arthritis- pain, swelling, warmth and tenderness of the involved joints; generalized and morning stiffness;
- insulin-dependent diabetes mellitus- insulinitis; this condition can lead to a variety of complications with an inflammatory component, including: retinopathy, neuropathy, nephropathy; coronary artery disease, peripheral
- 20       vascular disease, and cerebrovascular disease;
- autoimmune thyroiditis- weakness, constipation, shortness of breath, puffiness of the face, hands and feet, peripheral edema, bradycardia;
- multiple sclerosis- spasticity, blurry vision, vertigo, limb weakness, paresthesias;
- 25       • uveoretinitis- decreased night vision, loss of peripheral vision;
- lupus erythematosus- joint pain, rash, photosensitivity, fever, muscle pain, puffiness of the hands and feet, abnormal urinalysis (hematuria, cylinduria, proteinuria), glomerulonephritis, cognitive dysfunction, vessel thrombosis, pericarditis;
- 30       • scleroderma- Raynaud's disease; swelling of the hands, arms, legs and face; skin thickening; pain, swelling and stiffness of the fingers and knees, gastrointestinal dysfunction, restrictive lung disease; pericarditis;; renal failure;

- other arthritic conditions having an inflammatory component such as rheumatoid spondylitis, osteoarthritis, septic arthritis and polyarthritis- fever, pain, swelling, tenderness;
- 5     • other inflammatory brain disorders, such as meningitis, Alzheimer's disease, AIDS dementia encephalitis- photophobia, cognitive dysfunction, memory loss;
- other inflammatory eye inflammations, such as retinitis- decreased visual acuity;
- 10    • inflammatory skin disorders, such as , eczema, other dermatites (e.g., atopic, contact), psoriasis, burns induced by UV radiation (sun rays and similar UV sources)- erythema, pain, scaling, swelling, tenderness;
- inflammatory bowel disease, such as Crohn's disease, ulcerative colitis- pain, diarrhea, constipation, rectal bleeding, fever, arthritis;
- asthma- shortness of breath, wheezing;
- 15    • other allergy disorders, such as allergic rhinitis- sneezing, itching, runny nose
- conditions associated with acute trauma such as cerebral injury following stroke- sensory loss, motor loss, cognitive loss;
- heart tissue injury due to myocardial ischemia- pain, shortness of breath;
- 20    • lung injury such as that which occurs in adult respiratory distress syndrome- shortness of breath, hyperventilation, decreased oxygenation, pulmonary infiltrates;
- inflammation accompanying infection, such as sepsis, septic shock, toxic shock syndrome- fever, respiratory failure, tachycardia, hypotension, leukocytosis;
- 25    • other inflammatory conditions associated with particular organs or tissues, such as nephritis (e.g., glomerulonephritis)-oliguria, abnormal urinalysis; inflamed appendix- fever, pain, tenderness, leukocytosis; gout- pain, tenderness, swelling and erythema of the involved joint,
- 30    elevated serum                 and/or urinary uric acid;
- inflamed gall bladder- abdominal pain and tenderness, fever, nausea, leukocytosis;
- chronic obstructive pulmonary disease- shortness of breath, wheezing;

- congestive heart failure- shortness of breath, rales, peripheral edema;  
 Type II diabetes- end organ complications including cardiovascular,  
 ocular, renal, and peripheral vascular disease  
 lung fibrosis- hyperventilation, shortness of breath, decreased  
 5 oxygenation;  
 vascular disease, such as atherosclerosis and restenosis- pain, loss of  
 sensation, diminished pulses, loss of function  
 and alloimmunity leading to transplant rejection- pain, tenderness, fever.

- 10 Subclinical symptoms include without limitation diagnostic markers for  
 inflammation the appearance of which may precede the manifestation of clinical  
 symptoms. One class of subclinical symptoms is immunological symptoms, such  
 as the invasion or accumulation in an organ or tissue of proinflammatory  
 lymphoid cells or the presence locally or peripherally of activated pro-  
 15 inflammatory lymphoid cells recognizing a pathogen or an antigen specific to the  
 organ or tissue. Activation of lymphoid cells can be measured by techniques  
 known in the art.

- “Delivering” a therapeutically effective amount of an active ingredient to  
 a particular location within a host means causing a therapeutically effective blood  
 20 concentration of the active ingredient at the particular location. This can be  
 accomplished ,e.g., by local or by systemic administration of the active ingredient  
 to the host.

A “subject” or “a patient” or “a host” refers to mammalian animals,  
 preferably human.

- 25 Some of the preferred representative compounds according to the present  
 invention are specified below but should not construed to be limited thereto;

1. *3S*-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-  
 dioxoazolane
2. *(3R)*-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-  
 30 dioxoazolane
3. *(3S)*-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-methyl-2,5-  
 dioxoazolane
- 35 4. *(3S)*-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-  
 cyclopropylmethyl-2,5-dioxoazolane



5. (3*S*)-1-Cyclohexyl-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolane
- 5 6. (3*S*)-1-Cyanomethyl-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolane
7. Methyl 2-[(3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolan-1-yl]acetate
- 10 8. 2-[(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolan-1-yl]acetic acid
9. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-phenylazolane
- 15 10. (3*S*)-1-Benzyl-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolane
11. (3*S*)-1-[4-(*tert*-Butyl)benzyl]-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolane
- 20 12. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-cyanobenzyl)-2,5-dioxo-azolane
- 25 13. (3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-cyanobenzyl)-2, 5-dioxo-azolane
14. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(3-trifluoromethyl-benzyl)azolane
- 30 15. (3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(3-trifluoromethyl-benzyl)azolane
16. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(4-trifluoromethyl-benzyl)azolane
- 35 17. (3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(4-trifluoromethyl-benzyl)azolane
- 40 18. Ethyl 4-[(3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolan-1-yl]benzoate
19. Ethyl 3-[(3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolan-1-ylmethyl] benzoate
- 45 20. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-fluorobenzyl)-2, 5-dioxoazolane

21. (3*S*)-1-(3-Bromobenzyl)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2, 5-dioxo-azolane
- 5 22. (3*S*)-3-(3-Cyclopentyloxy)-4-methoxyphenylcarboxamido)-1-(2,5-dichlorobenzyl)-2, 5-dioxoazolane
23. (3*R*)-3-(3-Cyclopentyloxy)-4-methoxyphenylcarboxamido)-1-(2,5-dichlorobenzyl)-2, 5-dioxo-azolane
- 10 24. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(2,6-dichlorobenzyl)-2, 5-dioxoazolane
25. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-nitrobenzyl)-2, 5-dioxo-azolane
- 15 26. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(4-chloro-3-nitrobenzyl)-2, 5-dioxoazolane
27. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-pyridylmethyl)-2, 5-dioxo-azolane
- 20 28. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-oxopyridylmethyl)-2, 5-dioxoazolane
29. (3*S*)-1-Benzyl-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2-oxoazolane
- 25 30. (3*S*)-1-Benzyl-3-(3-cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2-oxoazolane
- 30 31. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-5-oxoazolane
32. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,6-dioxohexahydropyridine
- 35 33. (3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2,6-dioxohexahydro-pyridine
34. (3*R*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2,6-dioxo-hexahydro-pyridine
- 40 35. (3*S*)-3-(3-Cyclopropylmethyloxy-4-difluoromethoxyphenylcarboxamido)-2,6-dioxo-hexahydropyridine
36. (3*S*)-3-(4-Difluoromethoxy-3-methoxyphenylcarboxamido)-2,6-dioxohexahydro-pyridine
- 45 37. (3*S*)-3-[3,4-Di(difluoromethoxy)phenylcarboxamido]-2,6-dioxohexahydropyridine
- 50

38. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-ethyl-2,6-dioxohexahydro-pyridine
- 5 39. Ethyl 2-[(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,6-dioxohexahydro-1-pyridinyl]acetate
40. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(2,6-dichlorobenzyl)-2,6-dioxo-hexahydropyridine
- 10 41. (3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-1-(2,6-dichloro-benzyl)-2,6-dioxohexahydropyridine
42. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,6-dioxo-1-(4-pyridylmethyl)-hexahydropyridine
- 15 43. (3*S*)-3-[3,4-Di(difluoromethoxy)phenylcarboxamido]-1-(4-pyridylmethyl)-2,6-dioxo-hexahydropyridine
44. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2-oxohexahydropyridine
- 20 45. (3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2-oxohexahydropyridine
- 25 46. (3*S*)-3-(3-Cyclopropylmethyloxy-4-difluoromethoxyphenylcarboxamido)-2-oxohexahydro-pyridine
47. (3*S*)-3-[3,4-Di(difluoromethoxy)phenylcarboxamido]-2-oxohexahydropyridine
- 30 48. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2-oxo-1-phenylhexahydro-pyridine
49. (3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2-oxo-1-phenyl-hexahydropyridine
- 35 50. (3*S*)-3-(3-Cyclopropylmethyloxy-4-difluoromethoxyphenylcarboxamido)-2-oxo-1-phenyl-hexahydropyridine
- 40 51. (3*S*)-3-[3,4-Di(difluoromethoxy)phenylcarboxamido]-2-oxo-1-phenylhexahydropyridine
52. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-6-oxohexahydropyridine
- 45 53. (3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-6-oxohexahydropyridine
- 50 54. (3*S*)-3-(3-Cyclopropylmethyloxy-4-difluoromethoxyphenylcarboxamido)-6-oxo-hexahydropyridine

55. (3*S*)-3-[3,4-Di(difluoromethoxy)phenylcarboxamido]-6-oxohexahydropyridine
- 5 56. (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-6-oxo-1-phenylhexahydro-pyridine
- 10 57. (3*S*)-3-(3-Cyclopropylmethyloxy-4-difluoromethoxyphenylcarboxamido)-6-oxo-1-phenyl-hexahydropyridine
- Further preferred are
- 15 (3*S*)-1-[4-(*tert*-Butyl)benzyl]-3-(3-cyclopentyloxy-4-methoxyphenylcarbox-amido)-2,5-dioxoazolane;
- (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-cyanobenzyl)-2,5-dioxoazolane;
- 20 (3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(3-trifluoromethyl-benzyl)azolane;
- (3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(4-trifluoromethyl-benzyl)azolane;
- 25 (3*S*)-1-(3-Bromobenzyl)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2, 5-dioxoazolane;
- (3*R*)-3-(3-Cyclopentyloxy)-4-methoxyphenylcarboxamido)-1-(2, 5-dichlorobenzyl)-2, 5-dioxo-azolane;
- 30 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-nitrobenzyl)-2, 5-dioxo-azolane;
- (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(4-chloro-3-nitrobenzyl)-2, 5-dioxoazolane;
- 35 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-5-oxoazolane;
- (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,6-dioxohexahydropyridine;
- 40 (3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2,6-dioxohexahydro-pyridine;
- (3*R*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2,6-dioxo-hexahydropyridine;
- 45 (3*S*)-3-(3-Cyclopropylmethyloxy-4-difluoromethoxyphenylcarboxamido)-2,6-dioxohexahydropyridine;
- 50

(3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-6-oxohexahydropyridine; and

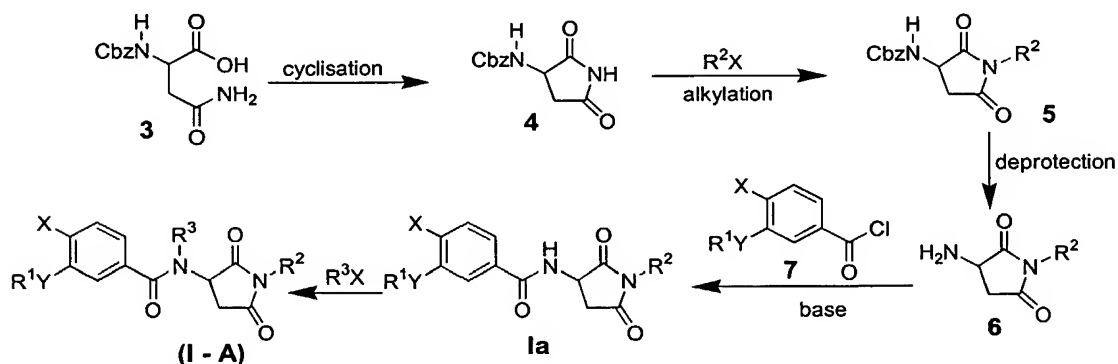
5 (3*S*)-3-(3-Cyclopropylmethyloxy-4-difluoromethoxyphenylcarboxamido)-6-oxo-hexahydropyridine

The compounds according to the invention may be prepared by the following processes. The symbols P, P<sup>1</sup>, R<sup>1</sup>, R<sup>2</sup> and A when used in the below formula below are to be understood to present those groups described above in  
10 relation to formula (I) unless otherwise indicated

In one embodiment the desired compounds of the formula (I) wherein X, R<sub>1</sub>, Y, and R<sub>2</sub>, R<sub>3</sub> are as defined above as described in the general description, can be synthesized as described in the general synthetic scheme 1.

15

### Scheme 1

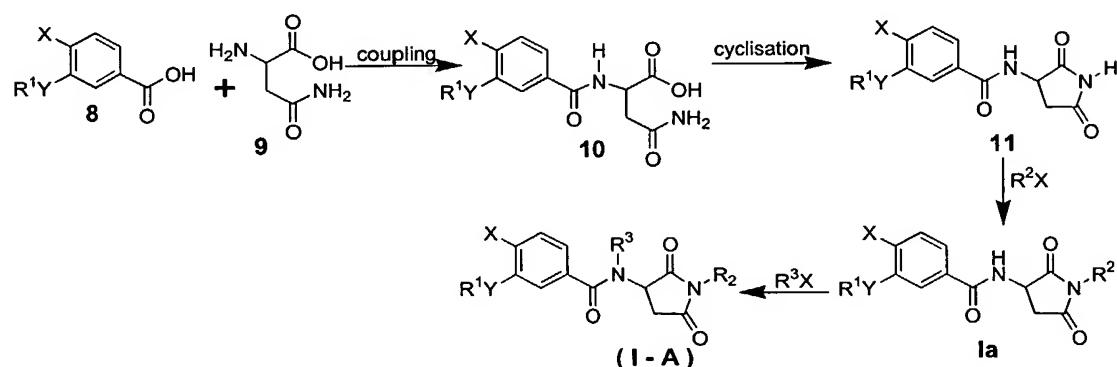


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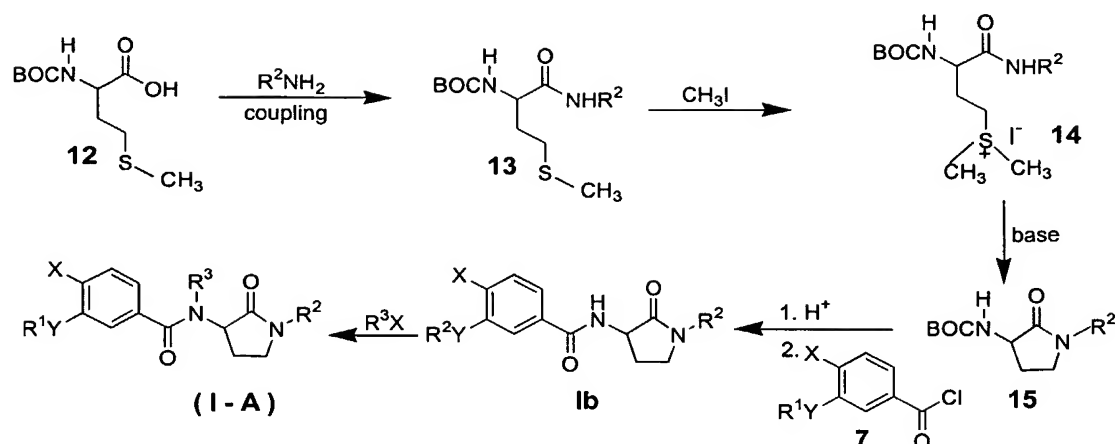
As shown in the above scheme 1, cyclisation of compound of general formula (3) by means of DCC in DMF at elevated temperature gives compound of general formula (4), which on selective alkylation with an alkyl halide of the general formula  $R^2X$ , yields compound of general formula (5). The compound of general formula (5) on deprotection by using palladium on carbon yields the amine of general formula (6). Condensation of the amine of general formula (6) with 3, 4-substituted benzoyl chloride of general formula (7) affords dioxoazolane of general formula (Ia). The compound (Ia) on substitution at benzamide nitrogen gives the novel compounds of general formula (I-A), wherein X,  $R^1$ , Y, and  $R^2$ ,  $R^3$  are as defined above.

Both racemic as well as pure enantiomers of I can be accessed by this approach depending on the stereochemical integrity of the amino acid used.

### Scheme 2



Alternatively, the compound of general formula (I-A) can be prepared by a linear approach as shown in scheme 2. As shown in the scheme 2, coupling of 3,4-substituted benzoic acid of general formula (8) with the compound of general formula (9) by means of coupling agents (carbodiimides, e.g., DCC, EDCA) with  
5 or without activators (e.g., HOBt and *N*-hydroxysuccinimide) gives acid amide of general formula (10). Cyclisation of compound of general formula (10) by means of using DCC and DMF gives 3-carboxamido-2, 5-dioxazoline of general formula (11) which on alkylation gives dioxazoline of general formula (Ia). The compound of general formula (Ia) on substitution at benzamide nitrogen gives the  
10 novel compounds of general formula (I-A), wherein X, R<sup>1</sup>, Y, and R<sup>2</sup>, R<sup>3</sup> are as defined above.

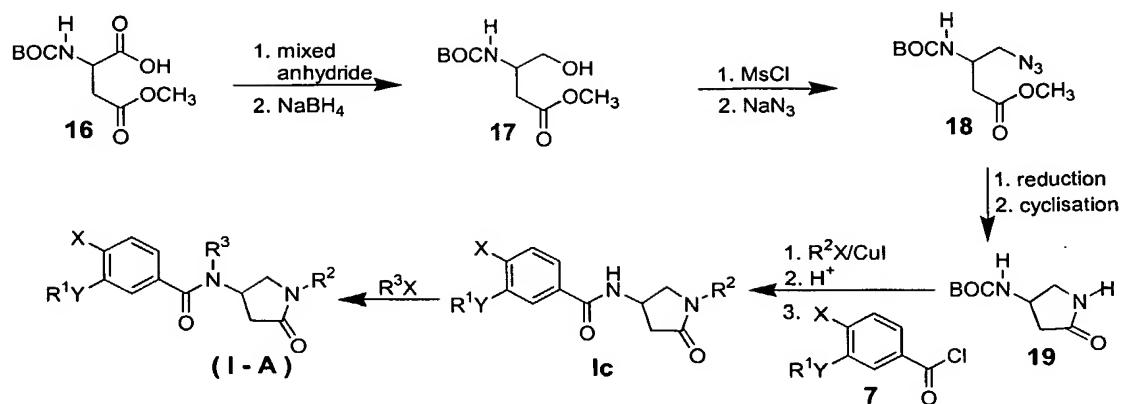
**Scheme 3**

5

Alternatively the following methodology can be used for the synthesis of compound of formula (I-A), condensation by coupling of compound of general formula (12) with amines of the general formula  $R^2NH_2$  provides amide of general formula (13). Reaction of compound of general formula (13) with methyl iodide results in the formation of sulfonium iodide with general formula (14), which under suitable basic reaction conditions undergo intramolecular cyclisation to give 2-oxoazolane of general formula (15). Deprotection of BOC group of formula (15) followed by coupling with acid chloride of formula (7) gives the amide of formula (1b). The compound of general formula (1b) on substitution at benzamide nitrogen gives the novel compounds of general formula (I-A), wherein X,  $R^1$ , Y, and  $R^2$ ,  $R^3$  are as defined above.

In yet another embodiment, the present invention relates to 3,4-substituted arylcarboxamido-5-oxoazolane having general formula I, wherein X,  $R_1$ , Y, and  $R_2$  are as defined above.



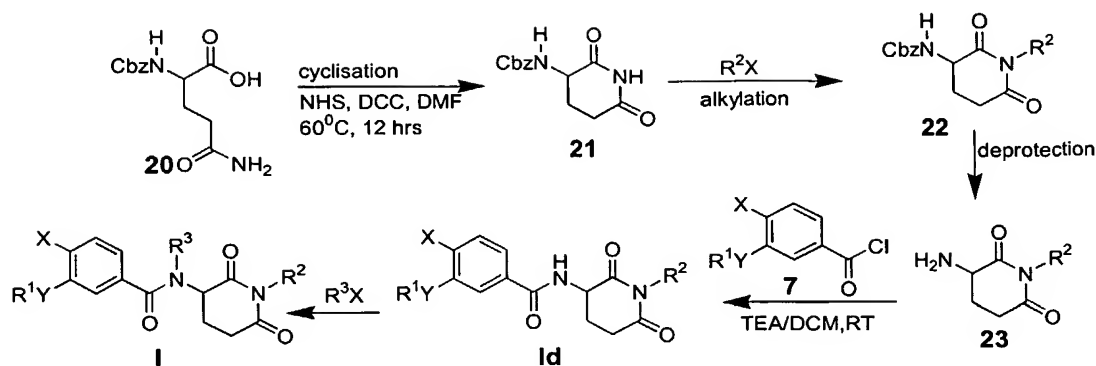
**Scheme 4**

5

In synthetic scheme 4 the following methodology can be used for the synthesis of novel compound of formula (I-A), reduction of carboxylic group of compound of general formula (16) via its mixed anhydride provides alcohol with the general formula (17). Mesylation of the compound (17) followed by treatment with sodium azide in DMSO gives azide having general formula (18). Palladium catalysed reductive cyclisation of compound of formula (18) gives azolane having general formula (19). Deprotection of (19) followed by its coupling with compound of general formula (7) affords compound of general formula (1c). The compound 1c on substitution at benzamide nitrogen gives the novel compounds of general formula (I-A), wherein X, R<sub>1</sub>, Y, and R<sub>2</sub>, R<sub>3</sub> are as defined above.

15

In yet another aspect, the present invention relates to 2,6-dioxypyridine derivative of the formula I, wherein X, R<sub>1</sub>, Y, and R<sub>2</sub> are as defined above.

**Scheme 5**

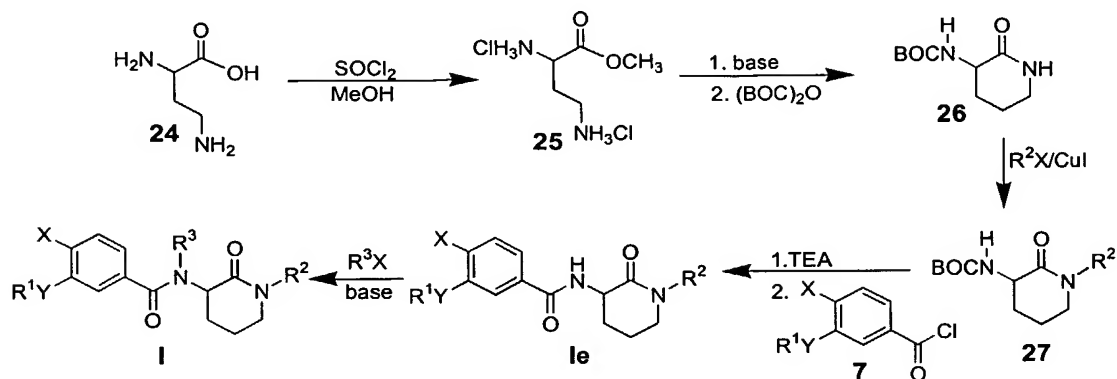
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The compounds of the general formula (**I-A**) can be obtained as follows, Cyclisation of compound of formula (**20**) using DCC and *N*-hydroxysuccinimide in DMF at elevated temperature gives 2,6-dioxypyridine derivative of formula (**21**), which is on treatment with alkyl halides of the general formula  $R^2X$  give *N*-1 substituted 2,6-dioxypyridine derivative of general formula (**22**). Palladium catalysed removal of Cbz protecting group of compound of general formula (**22**) gives compound of general formula (**23**). Compounds of general formula (**23**) on coupling with the compound of formula (**7**) by means of triethylamine in THF provides the compound of general formula (**Id**). The compound (**Id**) on substitution at benzamide nitrogen gives the novel compounds of general formula (**I-A**), wherein X,  $R_1$ , Y, and  $R_2$ ,  $R_3$  are as defined above.

**Scheme 6**

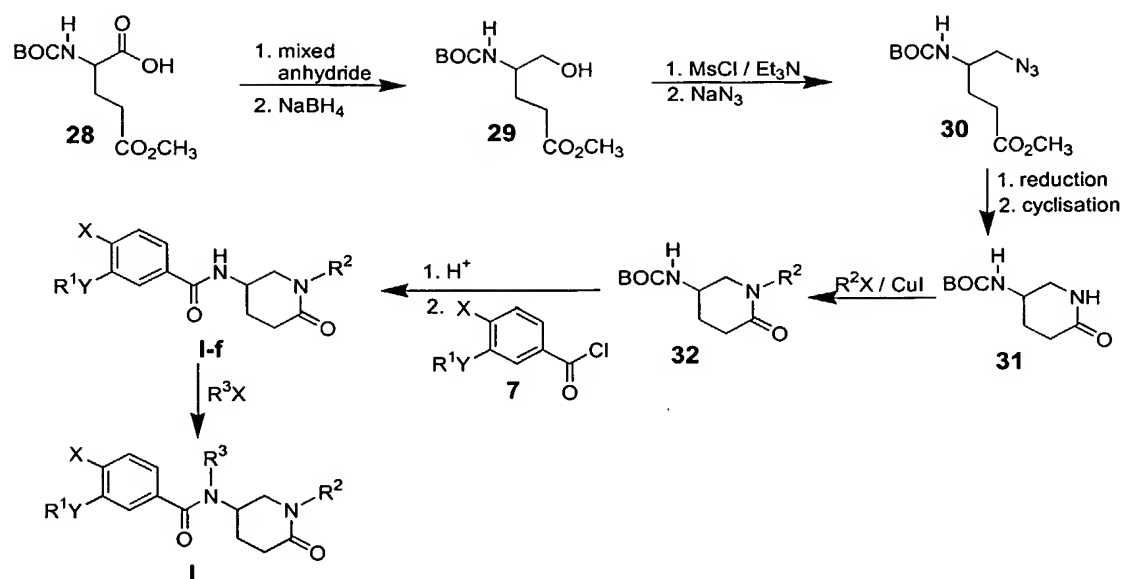
Another aspect of the present invention relates to 3-carboxamido-2-pyridones of the general formula I, wherein X, R<sub>1</sub>, Y, and R<sub>2</sub> are as defined above.

5



The novel compounds of formula I can be prepared as outlined in scheme 6. The compound of formula 24 on esterification by means of  $\text{SOCl}_2$  in methanol gives compound of formula 25 as its dihydrochloride salt. Intramolecular cyclisation of compound of formula 25 under basic conditions gives the compound of formula 26 as its BOC derivative. The ring nitrogen in compound 26 was selectively alkylated using alkyl halide in presence of  $\text{CuI}$  to give the compound of formula 27. Deprotection of compound of formula 27 followed by coupling with compound of formula 7 gives the compound of general formula 1e. The compound 1e on substitution at benzamide nitrogen gives the novel compounds of general formula I-A, wherein X, R<sub>1</sub>, Y, and R<sub>2</sub>, R<sub>3</sub> are as defined above.

Another aspect of the present invention relates to 3-carboxamido-6-pyridones of the general formula I, wherein X, R<sub>1</sub>, Y, and R<sub>2</sub> are as defined above.

**Scheme 7**

5

A method for the synthesis novel compounds of general formula (I-A) have been provided in scheme 7. Selective reduction of carboxylic acid group of compound of formula (28) via its mixed anhydride using  $\text{NaBH}_4$  gives the alcohol of general formula (29). This alcohol (29) is converted to the azide of general formula (30) via its mesylate. Azide (30) on treatment with  $\text{Pd/C}$  undergoes reduction and cyclization to get the compound of formula (31). The amide nitrogen of compound of formula (31) is alkylated with alkyl halides of the general formula  $\text{R}^2\text{X}$  under  $\text{CuI}$  catalysis give the compound of formula (32). Acylation of compound (32) with compound of formula (7) gives the compound of general formula **If**. The compound **If** on substitution at benzamide nitrogen gives the novel compounds of general formula (I – A), wherein  $\text{X}$ ,  $\text{R}_1$ ,  $\text{Y}$ , and  $\text{R}_2$ ,  $\text{R}_3$  are as defined above.

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuum and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent, e.g. in a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a

low molecular weight aliphatic alcohol (ethanol, isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by  
5 basification or by acidifying into the free compounds which, in turn can be converted into salts.

In general, the ethereal solvents used in the above described processes for the preparation of compounds of the formula (I) are selected from diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran, diisopropyl ether, 1,4 dioxane and the  
10 like. The chlorinated solvent which may be employed may be selected from dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like. The aromatic solvents which may be employed may be selected from benzene, toluene. The alcoholic solvents which may be employed may be selected from methanol, ethanol, n-propanol, isopropanol, tert.butanol and the like. The  
15 aprotic solvents which may be employed may be selected from N, N-dimethylformamide, dimethyl sulfoxide and the like.

In general, the compounds prepared in the above described processes are obtained in pure form by using well known techniques such as crystallization using solvents such as pentane, diethyl ether, isopropyl ether, chloroform,  
20 dichloromethane, ethyl acetate, acetone, methanol, ethanol, isopropanol, water or their combinations, or column chromatography using Alumina or silica gel and eluting the column with solvents such as hexane, petroleum ether (pet.ether), chloroform, ethyl acetate, acetone, methanol or their combinations.

Various polymorphs of a compound of general formula (I) forming part of  
25 this invention may be prepared by crystallization of compound of formula (I) under different conditions. example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures, various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the  
30 compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The present invention provides novel heterocyclic compounds, their analogs, their tautomers, their regioisomers, their stereoisomers, their

enantiomers, their diastereomers, their polymorphs, their pharmaceutically acceptable salts, their appropriate N-oxides and their pharmaceutically acceptable solvates.

The present invention also provides pharmaceutical compositions, containing compounds of the general formula (I) as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their enantiomers, their diastereomers, their pharmaceutically acceptable salts or their pharmaceutically acceptable solvates in combination with the usual pharmaceutically employed carriers, diluents and the like. The pharmaceutical compositions according to this invention can be used for the treatment of allergic disorders.

It will be appreciated that some of the compounds of the general formula (I) defined above according to the invention can contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centers in the compounds of the general formula (I) can give rise to stereoisomers and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers and their mixtures, including racemic mixtures.

The invention may also contain E & Z geometrical isomers wherever possible in the compounds of the general formula (I) which includes the single isomer or mixture of both the isomers

The pharmaceutical compositions may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like and may contain flavorants, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. The active compounds of the formula (I) will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage in the range as described above. Thus, for oral administration, the compounds of the formula (I) can be combined with a suitable solid, liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like. For parenteral administration, the compounds of the formula (I) can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in

sesame or peanut oil, aqueous propylene glycol and the like can be used as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds of the formula (I). The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, 5 subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

The compounds can also be administered by inhalation when application within the respiratory tract is intended. Formulation of the present compounds is especially significant for respiratory inhalation, wherein the compound of Formula 10 I is to be delivered in the form of an aerosol under pressure. It is preferred to micronize the compound of Formula I after it has been homogenised, e.g., in lactose, glucose, higher fatty acids, sodium salt of dioctylsulfosuccinic acid or, most preferably, in carboxyme3thyl cellulose, in order to achieve a microparticle size of 5  $\mu\text{m}$  or less for the majority of particles. For the inhalation formulation, 15 the aerosol can be mixed with a gas or a liquid propellant for dispensing the active substance. An inhaler or atomizer or nebulizer may be used. Such devices are known. See, e.g., Newman et al., *Thorax*, 1985, 40\_61-676; Berenberg, M., J. *Asthma USA*, 1985, 22:87-92; incorporated herein by reference in their entirety. A Bird nebulizer can also be used. See also U.S. Patents 6,402,733; 6,273,086; 20 and 6,228,346, incorporated herein by reference in their entirety. The compound of the structure I for inhalation is preferably formatted in the form of a dry powder with micronized particles. The compounds of the invention may also be used in a metered dose inhaler using methods disclosed in U.S. Patent 6, 131,566, incorporated herein by reference in its entirety.

25 In addition to the compounds of formula (I) the pharmaceutical compositions of the present invention may also contain or be co-administered with one or more known drugs selected from other clinically useful therapeutic agents.

The invention is explained in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit 30 the scope of the invention.

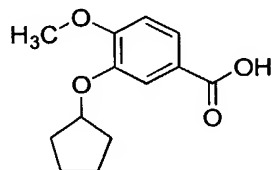
## Experimental

### Intermediates

#### Intermediate 1

#### 3-Cyclopentyloxy-4-methoxybenzoic acid

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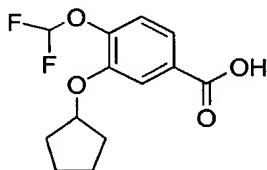
Step 1: A mixture containing 3-hydroxy-4-methoxybenzaldehyde (10 g, 65.72 mmol), anhydrous potassium carbonate (22.7 g, 164.31 mmol) and cyclopentyl bromide (11.75 g, 78.86 mmol) in dry DMF was stirred at 80 °C for 5 h. The reaction mixture was cooled to RT and filtered to remove the inorganic salts. The filtrate was diluted with water and extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were washed with water (3 x 100 ml), brine (50 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). Solvent was evaporated under reduced pressure to give 11.5 g (80 %) of the product as viscous brown liquid, which was used as such for step 2.

Step 2: To a stirred and cooled (-5 °C) solution of 3-cyclopentyloxy-4-methoxybenzaldehyde (11.0 g, 49.94 mmol) and sulphamic acid (7.27 g, 74.91 mmol) in 3:1 acetone-water mixture (200 ml) was added sodium chlorite (5.42 g, 59.92 mmol) dissolved in water (10 ml). The mixture was warmed to 10-15 °C and stirred at the same temperature for 3 h. The solid product separated out was collected by filtration. Crystallization of the crude product from acetone-water gave 9.2 g (78 %) of 3-cyclopentyloxy-4-methoxybenzoic acid as white crystals, mp 155-157 °C; IR (KBr) 2963-2535 (br), 1681, 1596, 1584, 1513, 1412, 1274, 1181 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.62-2.02 (m, 8 H), 3.81 (s, 1 H), 4.86-4.90 (m, 1 H), 7.20 (d, *J* = 8.4 Hz, 1 H), 7.67-7.70 (m, 2 H).



## Intermediate 2

## 3-Cyclopentyloxy-4-difluoromethoxybenzoic acid



5

Step-1: Prepared as described for intermediate 1 using 3-hydroxy-4-difluoromethoxy-benzaldehyde (5 g, 26.89 mmol), anhydrous potassium carbonate (7.4 g, 53.62 mmol) and cyclopentyl bromide (6 g, 40.26 mmol) in dry DMF (50 ml). The reaction yielded 6.8 g (100 %) of the product as viscous brown liquid which was used as such for step 2.

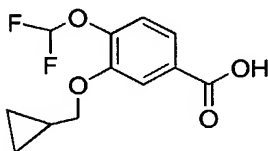
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Step 2: Oxidation of the aldehyde from step 1 with sodium chlorite (2.54 g, 28.08 mmol) and sulphamic acid (3.41g, 35.15 mmol) as described for intermediate 1, step 2 gave 4.8 g (75 %) of the product as white crystalline solid, IR (KBr) 2962, 2651, 1699, 1603, 1509, 1439, 1298, 1053, 763  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.62-2.03 (m, 8 H), 4.86-4.92 (m, 1 H), 6.62 (t,  $J = 75.0$  Hz, 1 H), 7.20 (d,  $J = 9.0$  Hz, 1 H), 7.67-7.70 (m, 2 H).

15

## Intermediate 3

## 20 3-Cyclopropylmethoxy-4-difluoromethoxybenzoic acid



25

Step 1: Prepared as described for intermediate 1, using 3-hydroxy-4-difluoromethoxy-benzaldehyde (5 g, 26.89 mmol), anhydrous potassium carbonate (7.4 g, 53.62 mmol) and bromomethyl cyclopropane (4.5 g, 33.3 mmol) in dry DMF (50 ml). The reaction yielded 5.5 g (82 %) of the product as viscous liquid which was used as such for step 2.

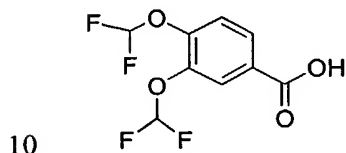
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Step 2: Oxidation of the aldehyde from step 1 with sodium chlorite (2.24 g, 24.75 mmol) and sulphamic acid (3.01 g, 31.03 mmol) as described for intermediate 1,

step 2 gave 4.16 g (78 %) of the product as white crystalline solid, mp 118-120 °C; IR (KBr) 2930, 1691, 1601, 1516, 1441, 1297, 1060, 765 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.36-0.41 (m, 2 H), 0.65-0.712 (m, 2 H), 1.2-1.37 (m, 1 H), 3.94(d, *J* = 6.6 Hz, 2 H), 6.72 (t, *J* = 74.7 Hz, 1 H), 7.22 (d, *J* = 8.1, Hz, 1 H), 7.65 (s, 1 H) 7.70 (d, *J* = 8.4 Hz, 1 H).

## Intermediate 4

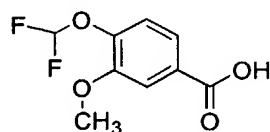
3,4-di(difluoromethoxy)benzoic acid



Oxidation of the 3,4-di(difluoromethoxy)benzaldehyde (5 g, 21.0 mmol) with sodium chlorite (2.28 g, 25.19 mmol) and sulphamic acid (3.05 g, 31.44 mmol) as described for intermediate 1, step 2 gave 4.9 g (91.8 %) of the product as white crystalline solid, mp x °C; IR (KBr) 3074-2538, 1700,1613, 1446, 1294, 1074, 916, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.58 (t, *J* = 72.6 Hz, 1 H), 6.62 (t, *J* = 72.6 Hz, 1 H), 7.33 (d, *J* = 9.0 Hz, 1 H), 7.99-8.02 (m, 2 H).

## Intermediate 5

20 4-Difluoromethoxy-3-methoxybenzoic acid



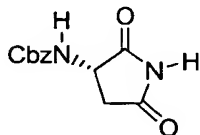
Step 1: Chlorodifluoromethane gas was bubbled into stirred slurry of 3-hydroxy-4-methoxybenzaldehyde (5 g, 32.89 mmol), anhydrous potassium carbonate (9.1 g, 65.94 mmol) in dry DMF (50 ml) at 70-80 °C for a period of 20 min. The reaction was further stirred at RT under chlorodifluoromethane gas atmosphere for 18 h. The reaction mixture was filtered to remove the inorganic salts. The filtrate was diluted with water and extracted with ethyl acetate (2 x 100 ml). The combined organic extracts were washed with water (3 x 100 ml), brine (50 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). Solvent was evaporated under reduced pressure to give 5 g

(75 %) of the product as a viscous brown liquid, which was used as such for step 2.

Step 2: Oxidation of the aldehyde from step 1 with sodium chlorite (2.69 g, 29.74 mmol) and sulphamic acid (3.60 g, 37.11 mmol) as described for intermediate 1, step 2 gave 4.8 g (89 %) of the product as white crystalline solid; IR (KBr) 2983, 2650, 1693, 1600, 1514, 1467, 1427, 1385, 1226, 1118, 1030  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.81 (s, 3 H), 6.62 (t,  $J = 74.0$  Hz, 1 H), 7.33 (d,  $J = 8.5$  Hz, 1 H), 7.99-8.02 (m, 2 H).

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Intermediate 6  
(3*S*)-3-(*N*-Cbz-Amino)azolane-2,5-dione

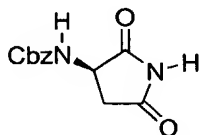


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To a stirred solution of *N*( $\alpha$ )-Cbz-L-asparagine (10 g, 37.5 mmol) dissolved in DMF (50 ml) was added DCC (7.8 g, 37.5 mmol) and *N*-hydroxysuccinimide (4.4 g, 37.5 mmol) and the mixture was heated at 80 °C for 6 h. DMF was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (100 ml) and filtered to remove DCU. The filtrate was washed with water (2 x 100 ml), brine (100 ml) and dried ( $\text{Na}_2\text{SO}_4$ ). The product obtained after evaporation of the solvent was purified by silica gel column chromatography using 50 % ethyl acetate in petroleum ether to give 4.2 g of the product as white solid, mp 66-69 °C; IR (KBr) 3395, 3177, 2936, 2749, 1723, 1689, 1519, 1260, 1177  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  2.81-2.89 (m, 1 H), 3.04-3.13 (m, 1 H), 4.33-4.40 (m, 1 H), 5.11 (s, 2 H), 4.63 (brs, 1 H), 7.34 (s, 5 H), 8.54 (brs, 1 H).

25

Intermediate 7  
(3*R*)-3-(*N*-Cbz-Amino)azolane-2,5-dione



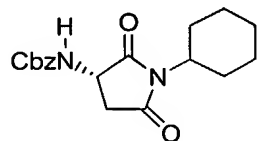
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Cyclisation of *N*( $\alpha$ )-Cbz-D-asparagine (10 g, 37.5 mmol) in the presence of DCC (7.8 g, 37.5 mmol) and *N*-hydroxysuccinimide (4.4 g, 37.5 mmol) in DMF (50 ml) as described above gave 4.2 g of the product as white solid, mp 66-69 °C;

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.80-2.89 (m, 1 H), 3.04-3.12 (m, 1 H), 4.33-4.41 (m, 1 H), 5.11 (s, 2 H), 4.61 (brs, 1 H), 7.34 (s, 5 H), 8.55 (brs, 1 H).

10

Intermediate 8  
(3*S*)-3-(*N*-Cbz-Amino)-1-cyclohexylazolane-2,5-dione



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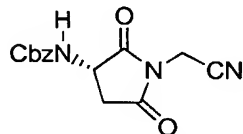
Step 1: A mixture of *N*-Cbz-L-aspartic acid (1.0 g, 3.745 mmol), DCC (0.77 g, 3.737 mmol), cyclohexylamine (480 mg, 4.848 mmol) and triethylamine (500 mg, x mmol) in dry THF (25 ml) was stirred at RT for 12 h. The mixture was filtered to remove the precipitated DCU and the filtrate was diluted with EtOAc (100 ml). The EtOAc solution was washed with water (2 x 100 ml), brine (50 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was evaporated under reduced pressure to give 900 mg a white solid which was used as such for the next step.

20

Step 2: A mixture of the above amide (750 mg, 2.155 mmol), DCC (445 mg, 2.160 mmol) and *N*-hydroxysuccinimide (250 mg, 2.173 mmol) in dry DMF (20 ml) was heated at 80 °C for 6 h. The mixture was evaporated under reduced pressure and the residue was diluted with EtOAc (100 ml). Filtered to remove DCU and the filtrate was concentrated under reduced pressure to give an oily residue which was purified by chromatography on silica gel using 25 % EtOAc in petroleum ether as eluent to give 350 mg of the product as white solid,

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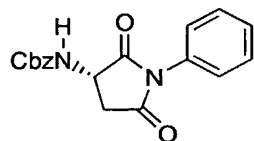
Intermediate 9  
(3*S*)-3-(*N*-Cbz-Amino)-1-cyanomethylazolane-2,5-dione



5

To a stirred solution of the solution (3*S*)-3-(*N*-Cbz-amino-2,5-dioxoazolane (550 mg, 2.215 mmol) in dry DMF (10 ml) was added cesium hydroxide monohydrate (446 mg, 2.658 mmol) and the mixture was stirred at rt for 10 min. Chloroacetonitrile (230 mg, 3.046 mmol) was added and further stirred at rt for 10 1.5 h. The reaction mixture was quenched with ice cold water and acidified with 1*N* HCl. The mixture was extracted with ethyl acetate (2 x 20 ml). The organic layer was washed with water (20 ml) and brine (20 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The crude product obtained after evaporation of the solvent was purified by silica gel column chromatography using 25 % EtOAc in petroleum ether as eluent to give 15 452 mg of the product as white solid; IR (KBr) 3370, 2949, 2242, 1721, 1523, 1261, 1171 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.91 (dd, *J* = 18.3, 5.7 Hz, 1 H), 3.15 (dd, *J* = 18.3, 9.2 Hz, 1 H), 4.30-4.37 (m, 1 H), 4.42 (s, 2 H), 5.05 (dd, *J* = 14.7, 12.0, 2 H), 5.58 (brs, 1 H), 7.32-7.39 (m, 5 H).

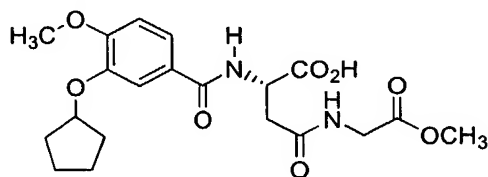
20 Intermediate 10  
(3*S*)-3-(*N*-Cbz-Amino)-1-phenylazolane-2,5-dione



25 Step 1: A mixture of *N*-Cbz-L-aspartic acid (1.0 g, 3.745 mmol), DCC (840 mg, 4.077 mmol), freshly distilled aniline (420 mg, 4.516 mmol) and triethylamine (500 mg, 4.950 mmol) in dry THF (20 ml) was stirred at RT for 12 h. The mixture was filtered to remove the precipitated DCU and the filtrate was diluted with EtOAc (100 ml). The EtOAc solution was washed with water (2 x 100 ml), brine 30 (50 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was evaporated under reduced pressure to give 450 mg of the amide as white solid, which was used as such for the next step.

Step 2: A mixture of the above amide (450 mg, 1.315 mmol), DCC (280 mg, 1.359 mmol) and *N*-hydroxysuccinimide (160 mg, 1.391 mmol) in dry DMF (10 ml) was heated at 80 °C for 6 h. The mixture was evaporated under reduced pressure and the residue was diluted with EtOAc (100 ml). Filtered to remove DCU and the filtrate was concentrated under reduced pressure to give an oily residue which was purified by chromatography on silica gel using 25 % EtOAc in petroleum ether as eluent to give 300 mg of the product as white solid, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.98 (dd, *J* = 18.3, 6.0 Hz, 1 H), 3.26 (dd, *J* = 18.0, 9.3 Hz, 1 H), 4.40-4.47 (m, 1 H), 5.12 (dd, *J* = 15.0, 12.0 Hz, 2 H), 5.58 (brs, 1 H), 7.31-7.46 (m, 10 H).

Intermediate 11  
(2*S*)-2-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-3-methyloxycarbonylmethyl-carbamoylpropanoic acid



This intermediate was prepared in two steps from L-aspartic acid as follows.

Steps 1: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared as follows: To a well stirred solution of 3-Cyclopentyloxy-4-methoxybenzoic acid (2.0 g, 8.474 mmol) in dry benzene (20 ml) was added oxalyl chloride (1.45 g, 12.711 mmol) at RT. The reaction was initiated with a drop of dry DMF and stirred at RT for 1 h under nitrogen atmosphere. The solvent was removed under reduced pressure to give the acid chloride quantitatively as a viscous residue, which was used as such for the coupling reaction.

Step 2: Preparation of (2*S*)-2-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)butane-dioic acid: To a stirred solution of L-aspartic acid in water was added potassium hydroxide (0.4 g, 7.142 mmol) and potassium carbonate (1.0 g, 7.246 mmol) at room temperature. A solution of acid chloride (step 1) in THF (30

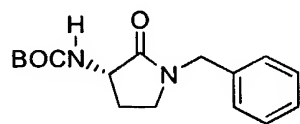
ml) was added drop-wise to the above solution and the mixture was stirred at RT for 24 h. The mixture was neutralized with aq. HCl to pH 2. The aqueous solution was extracted with EtOAc (2 x 100 ml). The EtOAc solution was washed with water (2x100 ml), brine (50 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The crude product obtained after evaporation of the solvent was purified by crystallization from diethyl ether to give 800 mg of the product as white solid, mp 145-148 °C; IR (KBr) 3299, 2962, 1709, 1631, 1506, 1274, 1230, 1140 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.60-1.67 (m, 2 H), 1.74-1.96 (m, 6 H), 2.94 (dq, *J* = 14.4, 7.5 Hz, 2 H), 3.85 (s, 3 H), 4.83-4.94 (m, 2 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 7.40-7.45 (m, 2 H).

10

Step 3: To a stirred solution of the above dicarboxylic acid (400 mg, 1.39 mmol) in dry THF (30 ml) was added DCC (260 mg, 1.262 mmol) and *N*-hydroxy succinimide (85 mg, 0.739 mmol) and the mixture was stirred at RT for 15 min. Glycine methyl ester (145 mg, 1.629 mmol) and triethylamine (1.0 g, 9.900 mmol) were added and the mixture was stirred at RT for 2 h. The mixture was filtered and the filtrate was diluted with EtOAc (100 ml). The EtOAc solution was washed with water (2 x 100 ml), brine (50 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The crude product obtained after evaporation of the solvent was purified by chromatography on silica gel using 50 % EtOAc in petroleum ether as eluent to give 120 mg of the product as white solid, mp 160-162 °C; IR (KBr) 3338, 3088, 2954, 1751, 1629, 1508, 1227, 1025 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.64-1.98 (m, 8 H), 2.79 (dd, *J* = 17.1, 6.9 Hz, 1 H), 3.14 (dd, *J* = 17.9, 5.7 Hz, 1 H), 3.72 (s, 3 H), 3.88 (s, 3 H), 4.04 (d, *J* = 5.4 Hz, 2 H), 4.81-4.88 (m, 1 H), 5.03-5.09 (m, 1 H), 6.84 (d, *J* = 8.2 Hz, 1 H), 7.30-7.40 (m, 2 H), 7.55 (d, *J* = 8.3 Hz, 1 H).

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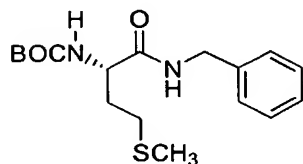
Intermediate 12  
(3*S*)-3-(*N*-BOC-Amino)-1-benzylazolan-2-one



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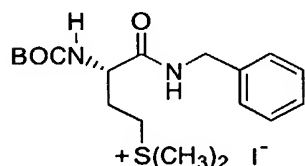
This intermediate was prepared in 3 steps from *N*-BOC-L- methionine as described below.

Step 1: Preparation of *N*-1-Benzyl-(2*S*)-2-amino-4-methylsulfanylbutanamide



5 To a stirred solution of BOC-methionine (1.0 g, 4.016 mmol) in DMF (10 ml) was added DCC (830 mg, 4.028 mmol) and *N*-hydroxy succinimide (490 mg, 4.260 mmol) and the mixture was stirred at room temperature for 30 min. Benzyl amine (850 mg, 7.943 mmol) and triethylamine (1.45 g, 14.376) were added to the mixture was stirred at room temperature for 12 h. The reaction mixture was  
10 diluted with EtOAc (150 ml) and filtered to remove the precipitated DCU. The filtrate was washed with 1*N* HCl (50 ml), water (100 ml) and brine (50 ml). The residue obtained after evaporation of the solvent was purified by crystallization from chloroform-hexane to yield 600 mg of the product as white solid; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.42 (s, 9 H), 1.88-2.03 (m, 1 H), 2.07 (s, 3 H), 2.08-2.18  
15 (m, 1 H), 2.46-2.63 (m, 2 H), 4.24-4.29 (m, 1 H), 4.44 (d, *J* = 5.7 Hz, 2 H), 5.18-5.22 (m, 1 H), 6.59 (brs, 1 H), 7.23-7.34 (m, 5 H).

Step 2: Preparation of (3*S*)-3-(*N*-BOC-amino)-3-benzylcarbamoylpropyl(dimethyl)-sulfonium iodide



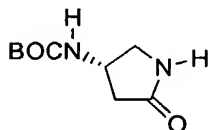
A mixture of *N*-benzyl methionine (550 mg, 1.627 mmol) and methyl iodide (5 ml, x mmol) in dichloromethane (10 ml) was stirred under nitrogen atmosphere  
25 for 6 h. The mixture was concentrated under reduced pressure to give 800 mg of the crude product as semisolid, IR (KBr) cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.41 (s, 9 H), 1.73-1.78 (m, 1 H), 2.54-2.62 (m, 1 H), 3.04 (s, 3 H), 3.22 (s, 3 H), 3.40-3.52 (m, 1 H), 3.68-3.76 (m, 1 H), 4.41 (d, *J* = 6.0 Hz, 2 H), 4.49 (m, 1 H), 6.09 (d, *J* = 6.6 Hz, 1 H), 7.21-7.35 (m, 5 H), 8.18 (brs, 1H).

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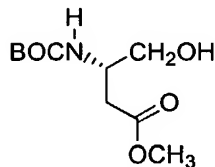
Step 3: (3*S*)-3-(*N*-BOC-Amino)-1-benzylazolan-2-one: To a stirred and cooled (0 °C) solution of sulfonium salt intermediate (800 mg, 1.66 mmol) in DMF (30 ml) was added sodium hydride (150 mg, 3.125 mmol) in one portion and the mixture was stirred at 0 °C - RT for 1 h. The reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl solution (50 ml) and extracted with EtOAc (2 x 100 ml). The combined organic extracts were washed with water (2 x 100 ml), brine (50 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The crude product obtained after evaporation of the solvent was purified by silica gel column chromatography using 25-30 % EtOAc in petroleum ether to give 450 mg of the product as white solid, mp x °C; IR (KBr) 3303, 2954, 1770, 1688, 1509, 1269, 1022 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.44 (s, 9 H), 1.77-1.88 (m, 1 H), 2.54-2.62 (m, 1 H), 3.19 (dd, *J* = 9.0, 6.0 Hz, 1 H), 4.15-4.22 (m, 1 H), 4.46 (d, *J* = 9 Hz, 2 H), 5.41 (brs, 1 H), 7.18-7.34 (m, 5 H).

Intermediate 13  
(3*S*)-3-(*N*-BOC-Amino)-5-oxoazolan-2-one



This intermediate was prepared in 3-steps from *N*-BOC-L-aspartic acid 4-methyl ester as described below

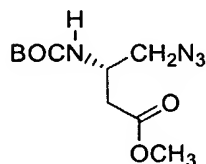
Step 1: Preparation of Methyl (3*S*)-3-(*N*-BOC-amino-4-hydroxybutanoate



Ethyl chloroformate (1.30 g, 11.981 mmol) was added to a well stirred solution of *N*-BOC-L-aspartic acid 4-methyl ester (2.8 g, 11.324 mmol) and *N*-methylmorpholine (1.21 g, 11.962 mmol) in dry THF (20 ml) at -10 °C. The reaction mixture was further stirred for 15 min at the same temperature. The reaction mixture was cooled to -15 °C and NaBH<sub>4</sub> (0.6 g, 15.860 mmol) was added in one portion. Dry methanol (10 ml) was added drop wise over a period of 20 min at the same temperature. The mixture was further stirred at -15 to -10 °C

for 30 min. The mixture was quenched with 1*N* hydrochloric acid to pH 2 and extracted with ethyl acetate (2 x 100 ml). The combined organic extracts were washed with water (3 x 100 ml), brine (50 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was evaporated under reduced pressure to give 1.6 g of the crude alcohol as a viscous liquid which was used as such for the next step.

Step 2: Methyl (3*S*)-3-(*N*-BOC-amino)-4-azidobutanoate



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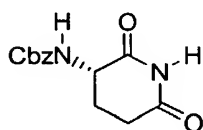
Methanesulfonyl chloride (1.17 g, 10.288 mmol) was added to a well-stirred and cooled (5 °C) solution of the above alcohol (1.6 g, 6.859 mmol) and triethylamine (2.07 g, 20.577 mmol) in dry dichloromethane (50 ml) under nitrogen atmosphere. The mixture was allowed to warm to RT over a period of 10 min and further stirred at RT for 3 h. The reaction was diluted with dichloromethane (100 ml) and washed with water (3 x 100 ml) followed by brine (50 ml). The extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was evaporated to give the crude mesylate, which was used as such for next step.

20 A mixture of crude mesylate from the above step and sodium azide (450 mg, 6.923 mmol) in dry DMF (50 ml) was stirred at 80 °C for 12 h under nitrogen atmosphere. The mixture was cooled to RT, diluted with water (150 ml) and extracted with ethyl acetate (2 x 100 ml). The combined EtOAc extracts were washed with water (2 x 100 ml) followed by brine (50 ml). The organic extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was evaporated under reduced pressure to give the crude product. This crude product was purified by silica gel column chromatography using 15 % EtOAc in petroleum ether to give 600 mg of the azide as a semisolid.

30 Step 3: To a solution of azido ester (600 mg, 2.323 mmol) in methanol (20 ml) was added 10 % Pd/C (20 mg) and the mixture was agitated under 40 psi

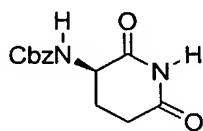
hydrogen gas pressure for 1 h in Paar hydrogenation apparatus. The reaction mixture was filtered through a celite bed and the filtrate was evaporated under reduced pressure to give the crude product. The crude product was purified by chromatography on silica gel using 10 % methanol in chloroform to give 200 mg of the product as white solid, mp 164-167 °C; IR (KBr) 3327, 2980, 1685, 1543, 1276, 1170 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.44 (s, 9 H), 2.19 (dd, *J* = 17.1, 5.2 Hz, 1 H), 2.68 (dd, *J* = 17.1, 8.1 Hz, 1 H), 3.24 (dd, *J* = 9.9, 4.2 Hz, 1 H), 3.70 (dd, *J* = 9.9, 6.3 Hz, 1 H), 4.36-4.42 (m, 1 H), 4.86 (brs, 1 H), 5.90 (brs, 1 H).

10 Intermediate 14  
(3*S*)-3-(*N*-Cbz-Amino)hexahydro-2,6-pyridinedione



15 To a stirred solution of *N*(α)-Cbz-L-glutamine (24 g, 85.71 mmol) in dry DMF (240 ml) was added DCC (19.5 g, 94.66 mmole) and *N*-hydroxysuccinimide (10.87g, 94.66 mmol) and the mixture heated at 80 °C for 18 h. The reaction mixture was cooled to RT and filtered to remove the precipitated DCU. The filtrate was diluted with EtOAc (100 ml) and washed with water (3 x 100 ml),  
20 brine (50 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The crude product obtained after evaporation of the solvent was purified by silica gel column chromatography using 30 % ethyl acetate in chloroform to give 15 g of the product as white solid, IR (KBr) 3424, 3257, 1708, 1679, 1527, 1194, 1038 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.81-1.95 (m, 1 H), 2.53-2.86 (m, 3 H), 4.30-4.39 (m, 1 H), 5.13 (s, 2 H), 6.68 (brs, 1 H, D<sub>2</sub>O exchangeable), 7.56 (s, 5 H), 8.16 (brs, 1 H, D<sub>2</sub>O exchangeable).  
25

Intermediate 15  
(3*R*)-3-(*N*-Cbz-Amino)hexahydro-2,6-pyridinedione

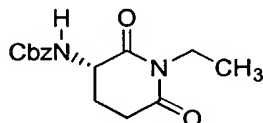


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Cyclastion of *N*(α)-Cbz-D-glutamine (4 g, 14.28 mmol) in presence of DCC (3.25 g, 15.77 mmol) and *N*-hydroxysuccinimide (1.81 g, 15.77 mmol) in dry

DMF (50 ml) as described above gave 2.5 g of the product as white solid; IR (KBr) 3424, 3257, 1708, 1679, 1527, 1194, 1038  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.82-1.94 (m, 1 H), 2.53-2.84 (m, 3 H), 4.30-4.40 (m, 1 H), 5.13 (s, 2 H), 6.67 (brs, 1 H,  $\text{D}_2\text{O}$  exchangeable), 7.58 (s, 5 H), 8.14 (brs, 1 H,  $\text{D}_2\text{O}$  exchangeable).

## Intermediate 16

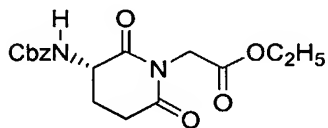
(3*S*)-3-(*N*-Cbz-Amino)-1-ethylhexahydro-2,6-pyridinedione

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A mixture of (3*S*)-3-(*N*-Cbz-Amino)hexahydro-2,6-pyridinedione (200 mg, 0.76 mmol), ethyl iodide (130 mg, 0.83 mmol), potassium carbonate (160 mg, 1.15 mmol) and tetrabutylammonium iodide (30 mg, 0.076 mmol) in dry acetone was stirred at RT for 48 h under nitrogen. The reaction mixture was diluted with water (100 ml) and extracted with EtOAc (2 x 50 ml). The combined organic extracts were washed with water (100 ml), brine (50 ml) and dried ( $\text{Na}_2\text{SO}_4$ ). The crude product obtained after evaporation of the solvent was purified by silica gel column chromatography using 30 % ethyl acetate in petroleum ether to give 130 mg of the product as white solid; IR (KBr) 3304, 2932, 1732, 1691, 1325, 1212  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.08-1.13 (t, 3 H), 1.72-1.87 (m, 1 H), 2.50-2.80 (m, 3 H), 3.71-3.90 (m, 2 H), 4.25-4.33 (m, 1 H), 5.12 (s, 2 H), 5.69 (s, 1 H), 7.35 (s, 5 H).

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## Intermediate 17

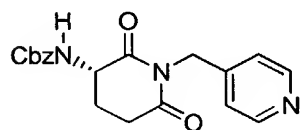
Ethyl 2-[(3*S*)-3-(*N*-Cbz-Amino)-2,6-dioxohexahydro-1-pyridinyl]acetate

5

- Alkylation of (3*S*)-3-(*N*-Cbz-Amino)hexahydro-2,6-pyridinedione (300 mg, 1.14 mmol) with ethyl bromoacetate (282 mg, 1.71 mmol), in the presence of potassium carbonate (240 mg, 1.34 mmol) and tetrabutylammonium iodide (45 mg, 0.11 mmol) in dry acetone (10 ml) as described in the case of intermediate 12 gave 250 mg (83 %) of the product as off-white solid, IR (KBr) 3273, 2958, 1752, 1734, 1693, 1554, 1266, 1166  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.26 (t,  $J = 7.5$  Hz, 3 H), 1.86-2.01 (m, 1 H), 2.52-2.94 (m, 3 H), 4.17 (q,  $J = 7.2$  Hz, 2 H), 4.41-4.57 (m, 3 H), 5.12 (s, 2 H), 5.66 (s, 1 H), 7.34 (s, 5 H).

15

## Intermediate 18

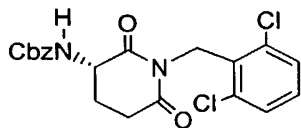
(3*S*)-3-(*N*-Cbz-Amino)-1-(4-pyridylmethyl)hexahydro-2,6-pyridinedione

20

- Alkylation of (3*S*)-3-(*N*-Cbz-Amino)hexahydro-2,6-pyridinedione (300 mg, 1.14 mmol), 4-with picolyl chloride hydrochloride (282 mg, 1.71 mmol) in the presence of potassium carbonate (475 mg, 3.44 mmol) and tetrabutylammonium iodide (30 mg, 0.076 mmol) in dry acetone (10 ml) as described in the case of intermediate 12 gave 300 mg of the product as white solid, IR (KBr) 3200, 2951, 1719, 1677, 1538, 1266, 1165  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.77-1.95 (m, 1 H), 2.51-2.96 (m, 3H), 4.33-4.40 (m, 1 H), 4.92 (q,  $J = 5.7$  Hz, 2 H), 5.12 (s, 2 H), 5.68 (s, 1 H), 7.18 (d,  $J = 5.7$  Hz, 2 H), 7.34 (s, 5 H), 8.50 (d,  $J = 5.7$  Hz, 2 H).

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## Intermediate 19

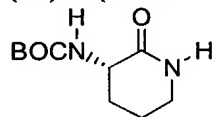
(3*S*)-3-(*N*-Cbz-Amino)-1-(2,6-dichlorobenzyl)hexahydro-2,6-pyridinedione

5

Alkylation of (3*S*)-3-(*N*-Cbz-Amino)hexahydro-2,6-pyridinedione (600 mg, 2.29 mmol) with 2,6-dichlorobenzyl bromide (660 mg, 2.75 mmol) in the presence of potassium carbonate (480 mg, 3.47 mmol) and tetrabutylammonium iodide (85 mg, 0.23 mmol) in dry acetone (10 ml) as described in the case of intermediate 12 gave 400 mg of the product as white solid; IR (KBr) 3250, 2901, 1705, 1687, 1520, 1432, 1230, 1020  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.75-1.90 (m, 1 H), 2.49-2.60 (m, 1 H), 2.67-2.92 (m, 2 H), 4.30-4.37 (m, 1 H), 5.09 (s, 1 H), 5.22 (d,  $J = 3.9$  Hz, 2 H), 5.66 (s, 1 H), 7.08-7.14 (m, 1 H), 7.24 (m, 6 H).

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## Intermediate 20

(3*S*)-3-(*N*-BOC-Amino)-2-oxohexahydropyridine

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Step 1: Freshly distilled thionyl chloride (10.60 g, 89.08 mmol) was added to the stirred slurry of L-Ornithine hydrochloride (5 g, 29.65 mmole) in dry methanol (50 ml) at room temperature to result a clear solution. The solution was refluxed for 1 h and excess thionyl chloride and methanol was removed under reduced pressure to give 7 g 5-Methyl (*S*)-2,5-diaminopentanoate dihydrochloride as a white solid, which was used as such for step 2.

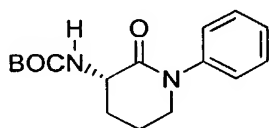
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Step 2: Triethylamine (12 g, 119 mmol) was added to a well-stirred solution of step 1 intermediate in methanol (200 ml) at room temperature and the mixture stirred for 1 h under nitrogen atmosphere. Di-*tert*-butyl dicarbonate (7.1 g, 32.56 mmol) in methanol (7 ml) was added to the reaction mixture and the mixture was stirred at RT for 18 h under nitrogen atmosphere. Methanol and excess reagents were evaporated under reduced pressure and the residue obtained was diluted with ethyl acetate (200 ml). This ethyl acetate solution was washed with water (3 x 300

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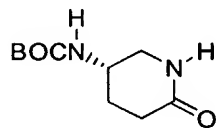
ml) followed by brine (100 ml) and dried over Na<sub>2</sub>SO<sub>4</sub>. This crude product obtained after evaporation of the solvent was purified by silica gel column chromatography using 1-2 % methanol in chloroform to give 3.8 g of (3*S*)-3-(*N*-BOC-Amino)-2-oxohexahydropyridine as semi solid, IR (neat) 3405, 3017, 1706, 1672, 1491, 1216, 1166, 986 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.42 (s, 9 H), 1.51-1.63 (m, 2 H), 1.83-1.95 (m, 2 H), 2.44 (m, 1 H), 3.28-3.33 (m, 2 H), 3.97-3.09 (m, 1 H), 5.40 (brs, 1 H, D<sub>2</sub>O exchangeable), 5.89 (brs, 1 H, D<sub>2</sub>O exchangeable).

10 Intermediate 21  
(3*S*)-3-(*N*-BOC-Amino)-1-phenyl-2-oxohexahydropyridine



15 A mixture containing (3*S*)-3-(*N*-BOC-Amino)-2-oxohexahydropyridine (2 g, 9.34 mmol), iodobenzene (2.3 g, 11.27 mmol), potassium phosphate (4 g, 18.84 mmol), copper(I)iodide (712 mg, 3.73 mmol), and 1,2-diaminoethane (224 mg, 3.73 mmol) in dry 1,4-dioxane (30 ml) was stirred at 100-110 °C for 24 h under nitrogen atmosphere. The reaction was cooled to RT and diluted with water (200 ml) and extracted with ethyl acetate (2 x 200 ml) and combined ethyl acetate solution was washed with water (3 x 200 ml) followed by brine solution (100 ml) then dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product obtained after evaporation of the solvent was purified by silica gel column chromatography using 2 % methanol in chloroform to give 1.8 g of the product as a white solid, IR (KBr) 3285, 2969, 1716, 1650, 1493, 1365, 1253, 1164, 767 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.45 (s, 9 H), 1.66-1.77 (m, 1 H), 1.99-2.08 (m, 2 H) 2.55-2.66 (m, 1 H), 3.67-3.72 (m, 2 H), 4.20-4.28 (m, 1 H), 5.52 (brs, 1 H, D<sub>2</sub>O exchangeable), 7.20-7.26 (m, 3 H), 7.34-7.39 (m, 2 H).

Intermediate 22  
(3*S*)-3-(*N*-BOC-Amino)-6-oxohexahydropyridine

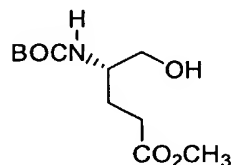


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This intermediate was prepared in 3 steps starting from *N*-BOC-L-glutamic acid 5-methyl ester as described below.

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Step 1: Preparation of Methyl (4*S*)-4-(*N*-BOC-amino) 5-hydroxypentanoate



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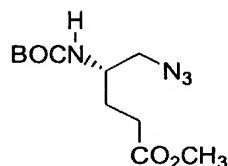
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Ethyl chloroformate (5.76 g, 53.07 mmol) was added to the well stirred solution of *N*-BOC-L-glutamic acid 5-methyl ester (12 g, 48.19 mmol) and *N*-methylmorpholine (5.4 g, 53.38 mmol) in dry THF (120 ml) at 0 °C for period of 10 min under nitrogen atmosphere. The reaction mixture was further stirred for 15 min at the same temperature. The reaction mixture was cooled to -15 °C and NaBH<sub>4</sub> (5.5 g, 145 mmol) was added in one portion. Dry methanol was added drop wise over a period of 20 min. at the same temperature. The mixture was further stirred at -15 to -10 °C for 30 min. The mixture was quenched with 1*N* hydrochloric acid and extracted with ethyl acetate (2 x 300 ml). The combines organic extracts were washed with water (3 x 600 ml), brine (300 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). This crude product obtained after evaporation of the solvent was purified by silica gel column chromatography using 2 % methanol in chloroform as eluent to give the alcohol (6.6 g) as a semisolid, IR (neat) 3367, 1977, 1692, 1525, 1452, 1367, 1250, 1171, 1058, 1030 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.43 (s, 9 H), 1.76-1.90 (m, 2 H), 2.41(dt, *J* = 5.4, 1.5 Hz, 2 H), 2.51 (brs, 1 H, D<sub>2</sub>O exchangeable), 3.54-3.65 (m, 2 H), 3.68 (s, 3 H), 4.81 (brs, 1 H, D<sub>2</sub>O exchangeable).



Step 2: Preparation of Methyl 5-azido-(4*S*)-4-(*N*-BOC-amino)pentanoate



- 5 Methanesulfonyl chloride (3.86 g, 33.71 mmol) was added to a well-stirred and cooled (5 °C) solution of the above alcohol (6.4 g, 25.91mmol) and triethylamine (5.3 g, 52.47 mmol) in dry dichloromethane (100 ml) under nitrogen atmosphere. The mixture was allowed to warm to RT over a period of 10 min and further stirred at RT for 30 min. The reaction was diluted with dichloromethane (100 ml)
- 10 and washed with water (3 x 200 ml) followed by brine (100 ml). The extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was evaporated to give the crude mesylate, which was used as such for next step.

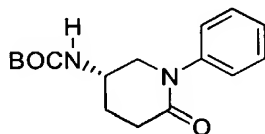
- A mixture of crude mesylate and sodium azide (2.02 g, 31.07 mmol) in dry DMF
- 15 (100 ml) was stirred at 60-70 °C for 18 h under nitrogen atmosphere. The mixture was cooled to RT, diluted with water (300 ml) and extracted with ethyl acetate (2 x 300 ml). The combined EtOAc extracts were washed with water (3 x 600 ml) followed by brine (300 ml). The organic extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was evaporated under reduced pressure to give the crude product. This
- 20 crude product was purified by silica gel column chromatography using 15 % EtOAc in petroleum ether to give the azide (3.9 g) as a semi solid, IR (KBr) 3341, 2989, 2097, 1732, 1682, 14446, 1303, 1249, 1166, 1060 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.44 (s, 9 H), 1.74-1.92 (m, 2 H), 2.40 (t, *J* = 7.5 Hz, 2 H), 3.36-3.43 (m, 2 H), 3.60 (s, 3 H), 3.70-3.77 (m, 1 H), 4.61 (br s, 1 H, D<sub>2</sub>O
- 25 exchangeable).

- Step 3: To a solution of azido ester (3.8 g, 14.73 mmol) in methanol (100 ml) was added 10 % Pd/C carbon (100 mg) and the mixture was agitated under 40 psi hydrogen pressure for 1 h in Paar hydrogenation apparatus. The reaction mixture
- 30 was filtered through a celite bed and the filtrate was evaporated under reduced pressure to give the pyridone (2.81 g) as a white solid, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.44 (s, 9 H), 1.79-1.92 (m, 1 H), 1.96-2.06 (m, 1 H), 2.46 (t, *J* = 6.9 Hz,

2 H), 3.12-3.18 (m, 1 H), 3.50-2.58 (m, 1 H), 3.93-4.01 (m, 1 H), 4.75 (brs, 3 H, D<sub>2</sub>O exchangeable), 6.19 (brs, 1 H, D<sub>2</sub>O exchangeable).

Intermediate 23

5 (3*S*)-3-(*N*-BOC-Amino)-1-phenyl-6-oxohexahydropyridone

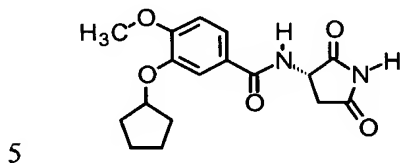


A mixture (3*S*)-3-(*N*-BOC-Amino)-6-oxohexahydropyridine (1.5 g, 7.01 mmol),  
 10 iodobenzene (1.60 g, 7.84 mmol), potassium phosphate (2.98 g, 14.02 mmol),  
 Cu(I)I (267 mg, 1.40 mmol), ethane 1,2-diamine (84 mg, 1.40 mmol) in dry 1,4-  
 dioxane (30 ml) was stirred at 100-110 °C for 48 h under nitrogen atmosphere.  
 The reaction mixture was cooled to RT and diluted with water (200 ml) and  
 extracted with ethyl acetate (2 x 200 ml). The combined organic extracts were  
 15 washed with water (3 x 200 ml) followed by brine solution (100ml) and dried  
 (Na<sub>2</sub>SO<sub>4</sub>). This crude product obtained after evaporation of the solvent was  
 purified by silica gel column chromatography using 1-2 % methanol in  
 chloroform to give the *N*-phenyl intermediate (900 mg) as white solid, IR (KBr)  
 3300, 2963, 1640, 1554, 1450, 1241, 1160, 1019, 794 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz,  
 20 CDCl<sub>3</sub>) δ 1.44 (s, 9 H), 1.87-1.97 (m, 1 H), 2.10-2.20 (m, 1 H), 2.64 (t, *J* = 6.9 Hz,  
 2 H), 3.50 (dd, *J* = 7.5, 4.5 Hz, 1 H), 3.85 (dd, *J* = 7.8, 3.9 Hz, 1 H), 4.05-4.20 (m,  
 1 H), 7.76 (d, *J* = 7.2 Hz, 1 H, D<sub>2</sub>O exchangeable), 7.19-7.26 (m, 3 H), 7.32-7.39  
 (m, 2 H).

## Examples

### Example - 1

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxazolane



Step 1: (3*S*)-3-Aminoazolane-2,5-dione was prepared as follows: To a solution of (3*S*)-3-(*N*-Cbz-amino)azolane-2,5-dione ( 4.0 g, 16.12 mmol) in methanol (40 ml) was added 5 % palladium on carbon (50 mg) and was stirred under 20 psi hydrogen pressure for 4 h. The mixture was filtered through a celite bed to remove the catalyst. The solvent was evaporated under reduced pressure to give 1.6 g of the product as pale yellow viscous liquid which was used as such for the next step.

Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared as follows: To a well stirred solution of 3-Cyclopentyloxy-4-methoxybenzoic acid (3.80 g, 16.10 mmol) in dry benzene (50 ml) was added oxalyl chloride (3.04 g, 24.12 mmol) at room temperature. The reaction was initiated with a drop of dry DMF and stirred at rt for 1 h under nitrogen atmosphere. The solvent was evaporated under reduced pressure to give the acid chloride quantitatively as a viscous residue, which was used as such for the coupling reaction.

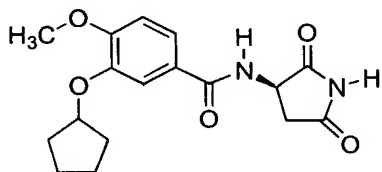
Step 3: Reaction of (3*S*)-3-Aminoazolane-2,5-dione with 3-Cyclopentyloxy-4-methoxybenzoyl chloride: The benzoyl chloride derivative (step 2) was added to a stirred solution of aminoazolane (step 1) and triethylamine (2.2 g, 21.782 mmol ) in dry DCM (100 ml) at 0 °C. The mixture was allowed to warm to room temperature over a period of 1 h. The crude product obtained after evaporation of the solvent was purified by chromatography on silica gel using 4 % methanol in chloroform as eluent to give 3.42 g (64 %) of the product as off-white solid, mp 230-232 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.60-1.91 (m, 8 H), 2.60 (dd, *J* = 12.0, 5.4 Hz, 1 H) , 2.92 (dd, *J* = 12.0, 9.0 Hz, 1 H), 3.78 (s, 3 H ), 4.48-4.58 (m,

1 H), 4.79-4.92 (m, 1 H), 7.00 (d,  $J = 8.4$  Hz, 1 H), 7.37 (s, 1 H), 7.44 (dd,  $J = 8.1, 1.2$  Hz, 1 H), 8.96 (d,  $J = 8.0$  Hz, 1 H), 11.25 (s, 1 H).

### Example 2

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(3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxazoline



- 10 Step 1: (3*R*)-3-Aminoazoline-2,5-dione was prepared by deprotection of (3*R*)-3-(*N*-Cbz-amino)azoline-2,5-dione (2.0 g, 8.06 mmol) using 5 % Pd/C (30 mg) in methanol (25 ml) under 20 psi hydrogen pressure for 4 h.

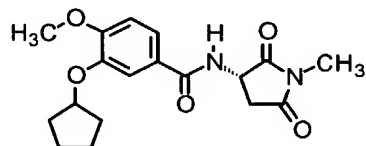
- Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared from 3-  
15 Cyclopentyloxy-4-methoxybenzoic acid (1.9 g, 8.05 mmol) using oxalyl chloride (1.5 g, 11.90 mmol) in dry benzene (30 ml) catalysed by DMF at RT.

- Step 3: Coupling Reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (1.2 g, 11.881 mmol) in dry DCM (50 ml) at 0°C. The  
20 crude product obtained was purified by silica gel column chromatography using 4 % methanol in chloroform to give 1.8 g (67 %) of the product as off-white solid, mp 230-232 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.60-1.91 (m, 8 H), 2.60 (dd,  $J = 12.0, 5.4$  Hz, 1 H), 2.92 (dd,  $J = 12.0, 9.0$  Hz, 1 H), 3.78 (s, 3 H), 4.48-4.58 (m, 1 H), 4.79-4.92 (m, 1 H), 7.00 (d,  $J = 8.4$  Hz, 1 H), 7.37 (s, 1 H), 7.44 (dd,  $J = 8.1,$   
25 1.2 Hz, 1 H), 8.96 (d,  $J = 8.0$  Hz, 1 H), 11.25 (s, 1 H).

**Example - 3**

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-methyl-2,5-dioxazolane

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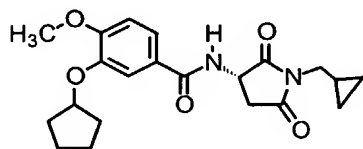


To a stirred solution of the solution (3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxazolane (150 mg, 0.45 mmol) in dry DMF (2 ml) was added cesium hydroxide monohydrate (80 mg, 0.45 mmol) and the mixture was stirred at rt for 10 min. Methyl iodide (130 mg, 0.9 mmol) was added and further stirred at rt for 1.5 h. The reaction mixture was quenched with ice cold water and acidified with 1*N* HCl. The mixture was extracted with ethyl acetate (2 x 20 ml). The combined organic layer was washed with water (20 ml) and brine (20 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The crude product obtained after evaporation of the solvent was purified by silica gel column chromatography using 2 % methanol in chloroform to give 60 mg (57 %) of the product as white solid, mp 104-107 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.59-1.96 (m, 8 H ), 2.90 (dd, *J* = 12.0, 6.1 Hz, 1 H), 3.09 (s, 3 H), 3.19 (dd, *J* = 12.0, 9.0 Hz, 1 H), 3.88 (s, 3 H), 4.44-4.51 (m, 1 H), 4.79-4.92 (m, 1 H), 6.73 (d, *J* = 6.2 Hz, 1 H), 6.83 (d, *J* = 6.2 Hz, 1 H), 7.26 (s, 1 H ), 7.35 (d, *J* = 2.0 Hz, 1 H); *m/z* 347 (MH<sup>+</sup>, 100 %), 219 (40).

**Example - 4**

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-cyclopropylmethyl-2,5-dioxazolane

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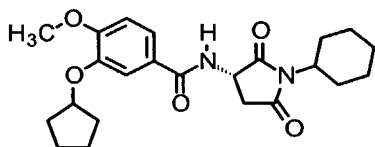


The reaction of (3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxazolane (100 mg, 0.30 mmol) with cyclopropylmethyl bromide (80 mg, 0.60 mmol) using cesium hydroxide (50 mg, 0.30 mmol) as described in example 3 followed by chromatography on silica gel (chloroform) gave 60 mg (52 %) of the

product as white solid, mp. 108-110 °C; IR (KBr) 3350, 3210, 2936, 2234, 1517, 1258  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.36-0.38 (m, 2 H), 0.49-0.55 (m, 2 H), 1.15-1.21 (m, 1 H), 1.58-1.98 (m, 8 H), 2.88 (dd,  $J = 12.0, 6.0$  Hz, 1 H), 3.22 (dd,  $J = 18.0, 9$  Hz, 1 H), 3.45 (d,  $J = 7.2$  Hz, 2 H), 3.87 (s, 3 H), 4.52-4.58 (m, 1 H), 4.79-4.83 (m, 1 H), 6.71 (d,  $J = 5.4$  Hz, 1 H), 6.83 (d,  $J = 8.4$ , 1 H), 7.28 (d,  $J = 2.4$  Hz, 1 H), 7.36 (d,  $J = 2.4$  Hz, 1 H).

### Example - 5

10 (3*S*)-1-Cyclohexyl-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxazolane



Step 1: (3*S*)-3-Amino-1-cyclohexylazolane-2,5-dione was prepared by  
15 deprotection of (3*S*)-3-(*N*-Cbz-amino)-1-cyclohexylazolane-2,5-dione (350 mg, 1.060 mmol) using 5 % Pd/C (25 mg) in methanol (25 ml) under 20 psi hydrogen pressure for 4 h.

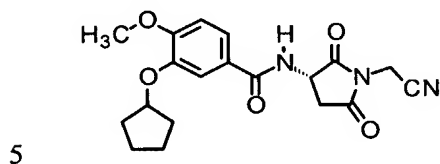
Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-methoxybenzoic acid (250 mg, 1.058 mmol) using oxalyl  
20 chloride (245 mg, 2.258 mmol) in dry benzene (10 ml) catalysed by DMF at RT.

Step 3: Coupling Reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (500 mg, 4.950 mmol) in dry DCM (50 ml) at 0 °C. The crude product obtained was purified by crystallization from diethyl ether to give 50 mg of the product as off-white solid, mp 135-138 °C; IR (KBr) 3294, 2933, 1776, 1704, 1649, 1504, 1268  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) 0.95-0.98 (m, 1 H), 1.21-1.48 (m, 7 H), 1.64-2.07 (m, 8 H), 2.19-2.32 (m, 1 H), 2.92 (dd,  $J = 18.0, 9.0$  Hz, 1 H), 3.24 (dd,  $J = 18.0, 9.0$  Hz, 1 H), 3.97 (s, 3 H), 4.09-4.17 (m, 1 H), 4.48-4.55 (m, 1 H), 4.89-4.92 (m, 1 H), 6.81 (d,  $J = 3.0$  Hz, 1 H), 6.91 (d,  $J = 9.0$  Hz, 1 H) 7.43 (s, 1 H), 7.45 (d,  $J = 3.0$  Hz, 1 H).

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**Example - 6**

(3*S*)-1-Cyanomethyl-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxazolane



Step 1: (3*S*)-3-Amino-1-cyanomethylazolane-2,5-dione was prepared by deprotection of (3*S*)-3-(*N*-Cbz-amino)-1-cyanomethylazolane (200 mg, 0.696 mmol) using 5 % Pd/C (15 mg) in methanol (10 ml) under 20 psi hydrogen pressure for 3 h.

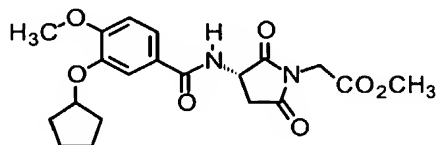
Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-methoxybenzoic acid (165 mg, 0.698 mmol) using oxalyl chloride (113 mg, 1.041 mmol) in dry benzene (5 ml) catalysed by DMF at RT.

Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (200 mg, 1.980 mmol) in dry DCM (10 ml) at 0 °C. The crude product obtained was purified by silica gel column chromatography using 25 % EtOAc in petroleum ether to give 80 mg of the product as white solid, mp 56-59 °C; IR (KBr) 3384, 2960, 2234, 1783, 1713, 1650, 1504, 1271, 1021 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.72-1.96 (m, 8 H ), 2.99 (dd, *J* = 18.0, 9.0 Hz, 1 H), 3.20 (dd, *J* = 18.0, 9.0 Hz, 1 H), 3.87 (s, 3 H), 4.46 (d, *J* = 3.0 Hz, 2 H), 4.46-4.53 (m, 1 H), 4.75-4.80 (m, 1 H), 6.82 (d, *J* = 9.0 Hz, 1 H), 7.09 (d, *J* = 6.2 Hz, 1 H), 7.25 (d, *J* = 1.8 Hz, 1 H), 7.30 (d, *J* = 1.8 Hz, 1 H); m/z 371 (MH<sup>+</sup>, 100 %).

**Example - 7**

Methyl 2-[(3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolan-1-yl]acetate

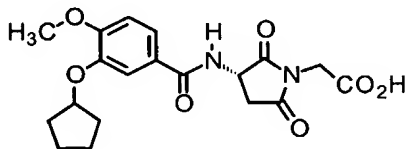
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To a stirred solution of (2*S*)-2-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-3-methoxy-carbonylmethylcarbamoylepropanoic acid (250 mg, 0.591 mmol) was added DCC (125 mg, 0.606 mmol) and *N*-hydroxysuccinimide (70 mg, 0.608 mmol) and the mixture was heated at 80 °C for 4 h. The mixture was evaporated under reduced pressure and the residue was diluted with EtOAc (100 ml). The EtOAc solution was washed with water (2 x 100 ml), brine (50 ml), and dried (Na<sub>2</sub>SO<sub>4</sub>). The crude product obtained after evaporation of the solvent was purified by chromatography on silica gel using 40 % EtOAc as eluent gave x mg of the product as white solid, mp 165-167 °C; IR (KBr) 3319, 2962, 1745, 1720, 1633, 1511, 1228 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.59-1.97 (m, 8 H), 2.96 (dd, *J* = 12.0, 6.0 Hz, 1 H), 3.26(dd, *J* = 18.0, 9.0 Hz, 1 H), 3.77 (s, 3 H), 3.87 (s, 3 H), 4.36 (s, 2 H), 4.63-4.70 (m, 1 H), 4.75-4.85 (m, 1 H), 6.82 (d, *J* = 9.0 Hz, 1 H), 6.91 (d, *J* = 6.0 Hz, 1 H), 7.27 (s, 1 H), 7.35 (d, *J* = 2.0 Hz, 1 H); *m/z* 347 (MH<sup>+</sup>, 100 %), 219 (40).

**Example - 8**

25 2-[(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolan-1-yl]acetic acid



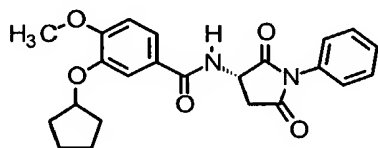
30 To a stirred solution of ester 7 (80 mg, 0.198 mmol) in methanol (5 ml) was added 2*N* sodium hydroxide solution (3 ml) and the mixture was stirred at room temperature for 2 h. Methanol was evaporated under reduced pressure and the



residue was diluted with EtOAc (50 ml) and water (50 ml). The mixture was acidified with 1N HCl to pH 2.0 and the layers were separated. The organic layer was washed with water (2 x 50 ml), brine (50 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The residue obtained after evaporation of the solvent was crystallized from MeOH-CHCl<sub>3</sub> to give 25 mg (32 %) of the product as white solid, mp 115-118 °C; IR (KBr) 3309, 2951, 2450, 1721, 1633, 1505, 1271 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.57-1.98 (m, 8 H), 2.76 (dd, *J* = 18.0, 12.0 Hz, 1 H), 3.12 (dd, *J* = 18.0, 9.0 Hz, 1 H), 3.79 (s, 3 H), 4.12 (dd, *J* = 1.2, 0.90 Hz, 2 H), 4.70-4.75 (m, 1 H), 4.75-4.86 (m, 1 H), 7.01 (d, *J* = 8.4 Hz, 1 H), 7.38 (d, *J* = 1.5 Hz, 1 H), 7.44 (d, *J* = 8.4 Hz, 1 H), 9.04 (d, *J* = 7.2 Hz, 1 H).

### Example - 9

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-phenylazolane



Step 1: (3*S*)-3-Amino-1-phenylazolane-2,5-dione was prepared by deprotection of (3*S*)-3-(*N*-Cbz-amino-1-phenylazolane-2,5-dione (300 mg, 0.924 mmol) using 5 % Pd/C (16 mg) in methanol (10 ml) under 20 psi hydrogen pressure for 3 h.

Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-methoxybenzoic acid (219 mg, 0.926 mmol) using oxalyl chloride (180 mg, 1.658 mmol) in dry benzene (5 ml) catalysed by DMF at RT.

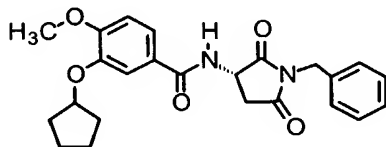
Step 3: Coupling Reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (250 mg, 2.475 mmol) in dry DCM (10 ml) at 0 °C. The crude product obtained was purified by silica gel column chromatography using 25 % EtOAc in petroleum ether to give 60 mg of the product as white solid, mp 150-152 °C; IR (KBr) 3293, 2957, 1716, 1630, 1502, 1268 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.59-2.01 (m, 8 H), 3.10 (dd, *J* = 18.0, 6.0 Hz, 1 H), 3.31

(dd,  $J = 18.0, 9.0$  Hz, 1 H), 3.87 (s, 3 H), 4.54-4.62 (m, 1 H), 4.79-4.83 (m, 1 H), 6.81 (d,  $J = 9.0$  Hz, 1 H), 6.96 (d,  $J = 6.0$  Hz, 1 H), 7.26-7.51 (m, 7 H).

### Example - 10

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(3*S*)-1-Benzyl-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxazoline



10

The reaction of (3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxazoline (90 mg, 0.270 mmol) with benzyl bromide (55 mg, 0.321 mmol) using cesium hydroxide (62 mg, 0.369 mmol) as described in example 3 followed by chromatography on silica gel (30 % EtOAc in petroleum ether) gave 58 mg (51 %)

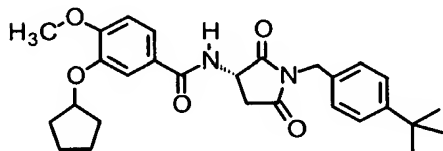
15 % of the product as white solid, mp 152-154 °C; IR (KBr) 3314, 2960, 1708, 1635, 1504, 1266, 1174  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.59-1.97 (m, 8 H), 2.88 (dd,  $J = 12.0, 6.0$  Hz, 1 H), 3.14 (dd,  $J = 12.0, 9.0$  Hz, 1 H), 3.86 (s, 3 H), 4.40-4.46 (m, 1 H), 4.74 (d,  $J = 3.3$  Hz, 2 H), 4.77-4.80 (m, 1 H), 6.78 (d,  $J = 8.4$  Hz, 1 H), 6.86 (d,  $J = 6.0$ , 1 H), 7.21-7.41 (m, 7 H).

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### Example - 11

(3*S*)-1-[4-(*tert*-Butyl)benzyl]-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxazoline

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The reaction of (3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxazoline (100 mg, 0.301 mmol) with 4-*tert*-butylbenzyl chloride (69 mg, 0.379 mmol) using cesium hydroxide (65 mg, 0.386 mmol) as described in example 3 followed by chromatography on silica gel (50 % EtOAc in petroleum ether) gave 76 mg (53 %) of the product as white solid, mp 98-100 °C; IR (KBr) 3385, 2961, 1712, 1649, 1503, 1268, 1166  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$

30

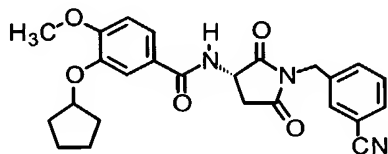
1.30 (s, 9 H ), 1.84-1.99 (m, 8 H), 2.92 (dd,  $J = 18.0, 6.0$  Hz, 1 H), 3.18 (dd,  $J = 18.0, 9.0$  Hz, 1 H), 3.88 (s, 3 H ), 4.46-4.53 (m, 1 H), 4.72 (d,  $J = 3.0$  Hz, 2 H), 4.77-4.82 ( m, 1 H ), 6.80 (d,  $J = 6.0$  Hz, 1 H), 6.84 (d,  $J = 3.0$  Hz, 1 H ), 7.24-7.36 (m, 6 H).

5

**Example - 12**

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-cyanobenzyl)-2,5-dioxo-azolane

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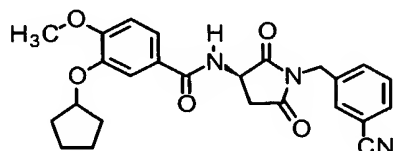


The reaction of (3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolane (75 mg, 0.225 mmol) with 3-cyanobenzyl bromide (70 mg, 0.358 mmol) using cesium hydroxide (46 mg, 0.273 mmol) as described in example 3 followed by chromatography on silica gel (3 % MeOH in chloroform) gave 47 mg (46.5 %) of the product as white solid, mp 92-95 °C; IR (KBr) 3319, 2933, 2231, 1710, 1648, 1503, 1269  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.73-2.09 (m, 8 H), 3.00 (dd,  $J = 12.0, 6.0$  Hz, 1 H ), 3.18 (dd,  $J = 18.0, 9.0$  Hz, 1 H), 3.89 (s, 3 H ), 4.41-4.48 (m, 1 H), 4.79 (d,  $J = 8.1$  Hz, 2 H), 4.83-4.85 (m, 1 H ), 6.80 (brs, 1 H ), 6.85 (d,  $J = 6.30$  Hz, 1 H), 7.28 (d,  $J = 1.8$  Hz, 1 H ), 7.38 (d,  $J = 1.8$  Hz, 1 H ), 7.45 (t,  $J = 7.5$  Hz, 1 H ), 7.58 (d,  $J = 8.1$  Hz, 1 H ), 7.68 (d,  $J = 8.1$  Hz, 1 H ) 7.77 (s, 1 H).

**Example - 13**

(3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-cyanobenzyl)-2,5-dioxo-azolane

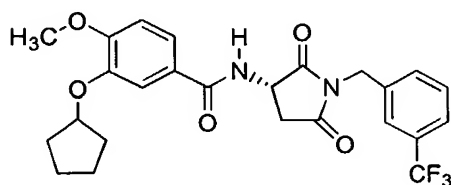
5



The reaction of (3*R*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolane (100 mg, 0.300 mmol) with 3-cyanobenzyl bromide (71 mg, 0.364 mmol) using cesium hydroxide (61 mg, 0.363 mmol) as described in example 3 followed by chromatography on silica gel (3 % MeOH in chloroform) gave 60 mg (44.5 %) of the product as white solid, mp 115-120 °C; IR (KBr) 3322, 2933, 2231, 1710, 1648, 1503, 1269 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.79-2.04 (m, 8 H), 2.99 (dd, *J* = 18.0, 9.0 Hz, 1 H), 3.17 (dd, *J* = 18.0, 9.0 Hz, 1 H), 3.88 (s, 3 H), 4.39-4.46 (m, 1 H), 4.71-4.83 (m, 3 H), 6.75 (d, *J* = 9.0 Hz, 1 H), 6.83 (d, *J* = 9.0 Hz, 1 H), 7.26 (d, *J* = 3.6 Hz, 1 H), 7.36 (d, *J* = 2.1 Hz, 1 H), 7.43 (t, *J* = 8.4 Hz, 1 H), 7.57 (dt, *J* = 8.4, 3.6 Hz, 1 H), 7.65 (d, *J* = 9.0 Hz, 1 H), 7.76 (s, 1 H)

20 **Example 14**

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(3-trifluoromethylbenzyl)azolane



25

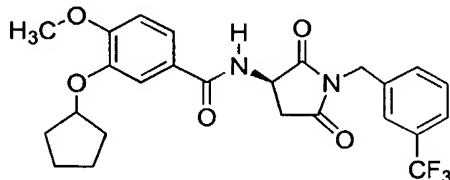
The reaction of (3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolane (150 mg, 0.451 mmol) with 3-trifluoromethylbenzyl bromide (135 mg, 0.564 mmol) using cesium hydroxide (91 mg, 0.541 mmol) as described in example 3 followed by chromatography on silica gel (40 % EtOAc in petroleum ether) gave 65 mg (29 %) of the product as a white solid, IR (KBr) 3389, 2960, 1711, 1582, 1563, 1329, 1270, 1166, 1020 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.79-1.99

(m, 8 H), 2.97(dd,  $J = 17.7, 5.7$  Hz, 1 H), 3.17 (dd,  $J = 17.7, 9.1$  Hz, 1 H), 3.88 (s, 3 H), 4.41-4.48 (m, 1 H), 4.74-4.86 (m, 3 H) 6.74 (d,  $J = 6.3$  Hz, 1 H), 6.82 (d,  $J = 8.4$  Hz, 1 H), 7.22-7.26 (m, 1 H), 7.36 (d,  $J = 2.1$  Hz, 1 H) 7.44 (t,  $J = 7.8$  Hz, 1 H), 7.55 (d,  $J = 8.1$  Hz, 1 H), 7.61 (d,  $J = 7.5$  Hz, 1 H), 7.70 (s, 1 H).

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### Example 15

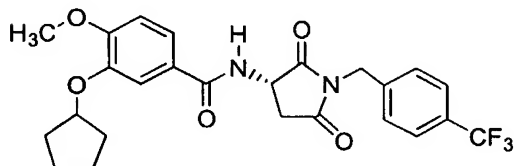
(3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(3-trifluoromethyl-benzyl)azolane



The reaction of (3*R*)-3-(3-cyclopentylloxy-4-methoxyphenylcarboxamido)-2,5-dioxazoline (150 mg, 0.451 mmol) with 3-trifluoromethylbenzyl bromide (135 mg, 0.564 mmol) using cesium hydroxide (91 mg, 0.541 mmol) as described in example 3 followed by chromatography on silica gel (50 % EtOAc in petroleum ether) gave 80 mg (36 %) of the product as white solid, IR (KBr) 3385, 2960, 1712, 1504, 1328, 1165, 1125, 1019  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.79-1.99 (m, 8 H), 2.97 (dd,  $J = 17.7, 5.7$  Hz, 1 H), 3.17 (dd,  $J = 17.7, 9.1$  Hz, 1 H), 3.88 (s, 3 H), 4.41-4.48 (m, 1 H), 4.74-4.86 (m, 3 H) 6.74 (d,  $J = 6.3$  Hz, 1 H), 6.82 (d,  $J = 8.4$  Hz, 1 H), 7.22-7.26 (m, 1 H), 7.36 (d,  $J = 2.1$  Hz, 1 H), 7.44 (t,  $J = 7.8$  Hz, 1 H), 7.55 (d,  $J = 8.1$  Hz, 1 H), 7.61 (d,  $J = 7.5$  Hz, 1 H), 7.70 (s, 1 H).

### **Example 16**

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(4-trifluoromethyl-benzyl)azolane

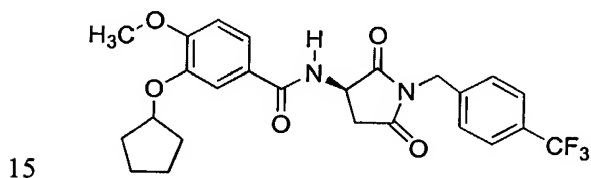


The reaction of (3*S*)-3-(3-cyclopentyloxy-4-methoxyphenyl-carboxamido)-2,5-dioxazolane (150 mg, 0.451 mmol) with 4-trifluoromethyl benzyl bromide (135

mg, 0.564 mmol) using cesium hydroxide (91 mg, 0.541 mmol) as described in example 3 followed by chromatography on silica gel (50 % EtOAc in petroleum ether) gave 68 mg (30 %) of the product as white solid, IR (KBr) 3344, 2966, 1712, 1633, 1504, 1330, 1174, 1019  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.61-1.99 (m, 8 H), 2.96 (dd,  $J = 17.7, 5.7$  Hz, 1 H), 3.17 (dd,  $J = 18.3, 8.7$  Hz, 1 H), 3.87 (s, 3 H), 4.41-4.48 (m, 1 H), 4.74-4.85 (m, 3 H), 6.73 (d,  $J = 6.3$  Hz, 1 H), 6.82 (d,  $J = 8.7$  Hz, 1 H), 7.22-7.26 (m, 1 H), 7.34 (d,  $J = 2.1$  Hz, 1 H) 7.53 (d,  $J = 8.4$  Hz, 2 H), 7.58 (d,  $J = 8.4$  Hz, 2 H),

### 10 Example 17

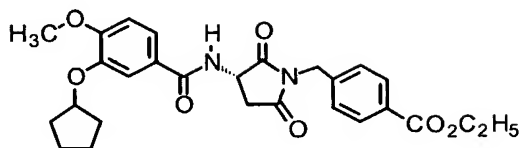
(3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(4-trifluoromethyl-benzyl)azolane



The reaction of (3*R*)-3-(3-cyclopentyloxy-4-methoxyphenyl-carboxamido)-2,5-dioxoazolane (150 mg, 0.451 mmol) with 4-trifluoromethyl benzyl bromide (135 mg, 0.564 mmol) using cesium hydroxide (91 mg, 0.541 mmol) as described in example 3 followed by chromatography on silica gel (50 % EtOAc in petroleum ether) gave 82 mg (37 %) of the product as a white solid, IR (KBr) 3349, 2964, 1712, 1504, 1329, 1168, 1019  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.61-1.99 (m, 8 H), 2.96 (dd,  $J = 17.7, 5.7$  Hz, 1 H), 3.17 (dd,  $J = 18.3, 8.7$  Hz, 1 H), 3.87 (s, 3 H), 4.41-4.48 (m, 1 H), 4.74-4.85 (m, 3 H) 6.73 (d,  $J = 6.3$  Hz, 1 H), 6.82 (d,  $J = 8.7$  Hz, 1 H), 7.22-7.26 (m, 1 H), 7.34 (d,  $J = 2.1$  Hz, 1 H) 7.53 (d,  $J = 8.4$  Hz, 2 H), 7.58 (d,  $J = 8.4$  Hz, 2 H).

### Example - 18

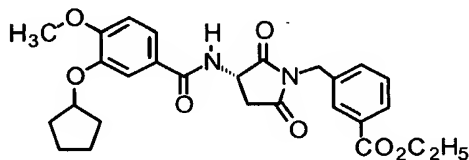
30 Ethyl 4-[(3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolan-1-yl]benzoate



The reaction of (3*S*)-3-(3-(3-cyclopentyloxy-4-methoxyphenyl)-carboxamido)-2,5-dioxazolan-1-ylmethyl benzoate (100 mg, 0.301 mmol) with ethyl 4-bromomethyl benzoate (130 mg, 0.534 mmol) using cesium hydroxide (70 mg, 0.416 mmol) as described in example 3 followed by chromatography on silica gel (20 % EtOAc in petroleum ether) gave 80 mg (52 %) of the product as white solid, mp 79-82 °C; IR (KBr) 3389, 2959, 1793, 1727, 1658, 1504, 1269, 1170 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.38 (t, *J* = 9.0 Hz, 3 H), 1.88-2.00 (m, 8H), 2.83-2.99 (m, 1 H), 3.12-3.22 (m, 1 H), 3.87 (s, 3 H), 4.35 (q, *J* = 6.0 Hz, 2 H), 4.43-4.50 (m, 1 H), 4.73-4.84 (m, 3 H), 6.79-6.83 (m, 2 H), 7.23-7.27 (m, 3 H), 7.34 (d, *J* = 2.1 Hz, 1 H), 7.46 (d, *J* = 9.9 Hz, 1 H), 7.98 (dd, *J* = 9.9, 2.1 Hz, 1 H).

#### Example - 19

Ethyl 3-[(3*S*)-3-(3-(3-cyclopentyloxy-4-methoxyphenyl)carboxamido)-2,5-dioxazolan-1-ylmethyl] benzoate



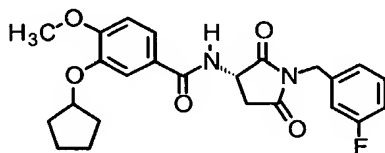
The reaction of (3*S*)-3-(3-(3-cyclopentyloxy-4-methoxyphenyl)carboxamido)-2,5-dioxazolan-1-ylmethyl benzoate (100 mg, 0.301 mmol) with ethyl 3-bromomethyl benzoate (130 mg, 0.534 mmol) using cesium hydroxide (70 mg, 0.416 mmol) as described in example 3 followed by chromatography on silica gel (20 % EtOAc in petroleum ether) gave 85 mg (55.5 %) of the product as white solid, mp 75-80 °C; IR (KBr) 3386, 2959, 1713, 1649, 1503, 1269 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.38 (t, *J* = 6.9, 3 H), 1.78-1.97 (m, 8 H), 2.92 (dd, *J* = 18.0, 6.0 Hz, 1 H), 3.18 (dd, *J* = 18.0, 6.0 Hz, 1 H), 3.87 (s, 3 H), 4.35 (q, *J* = 7.28, 2 H), 4.48-4.55 (m, 1 H), 4.73-4.84 (m, 1 H), 4.80 (d, *J* = 6.0 Hz, 2 H), 6.81 (d, *J* = 8.7 Hz, 1 H), 6.85 (d, *J*

= 6.0 Hz, 1 H ), 7.26 (d,  $J$  = 1.8 Hz, 1 H ), 7.35 (d,  $J$  = 1.8 Hz, 1 H ), 7.39 (t,  $J$  = 7.8 Hz, 1 H ), 7.60 (d,  $J$  = 7.8 Hz, 1 H), 7.95 (d,  $J$  = 6.0 Hz, 1 H ), 8.03 (s, 1 H).

### Example - 20

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(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-fluorobenzyl)-2,5-dioxoazolane



10

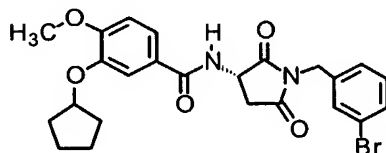
The reaction of (3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolane (100 mg, 0.301 mmol) with 3-fluorobenzyl bromide (120 mg, 0.634 mmol) using cesium hydroxide (65 mg, 0.386 mmol) as described in example 3 followed by chromatography on silica gel (30 % EtOAc in petroleum ether) gave 65 mg (49 %) of the product as white solid, mp 72-74 °C; IR (KBr) 3381, 2958, 1712, 1503, 1400, 1334, 1269 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.78-2.06 (m, 8 H), 2.93 (dd,  $J$  = 12.0, 9.0 Hz, 1 H), 3.18 (dd,  $J$  = 12.0, 9.0 Hz, 1 H), 3.87 (s, 3 H), 4.43-4.50 (m, 1 H), 4.73 (d,  $J$  = 5.4 Hz, 2 H), 4.77-4.83 (m, 1 H), 6.78-6.83 (m, 2 H), 6.98 (t,  $J$  = 2.7 Hz, 1 H), 7.11-7.19 (m, 2 H), 7.22-7.35 (m, 3 H).

20

### Example - 21

(3*S*)-1-(3-Bromobenzyl)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolane

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The reaction of (3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolane (100 mg, 0.301 mmol) with 3-bromobenzyl bromide (115 mg, 0.45 mmol) using cesium hydroxide (55 mg, 0.33 mmol) as described in example 3 followed by chromatography on silica gel (50 % EtOAc in petroleum ether) gave 75 mg (54 %) of the product as off-white solid, mp. 184-186 °C; IR (KBr) 3304,

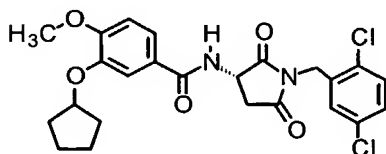
30



2958, 1714, 1634, 1504, 1394, 1272, 1178  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.58-1.99 (m, 8 H), 2.89 (dd,  $J = 15.0, 9.0$  Hz, 1 H), 3.10 (dd,  $J = 18.0, 9.0$  Hz, 1 H), 3.81 (s, 3 H), 4.34-4.41 (m, 1 H), 4.65 (d,  $J = 6.0$  Hz, 2 H), 4.71-4.75 (m, 1 H), 6.73 (d,  $J = 9.0$  Hz, 1 H), 6.88 (d,  $J = 6.0$  Hz, 1 H), 7.10-7.36 (m, 5 H), 7.52 (s, 1 H).

### Example - 22

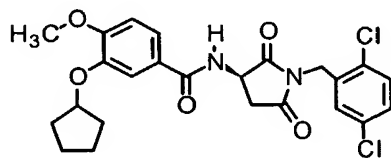
(3*S*)-3-(3-Cyclopentyloxy)-4-methoxyphenylcarboxamido)-1-(2, 5-dichlorobenzyl)-2, 5-dioxoazolane



The reaction of (3*S*)-3-(3-cyclopentyloxy)-4-methoxyphenylcarboxamido)-2,5-dioxoazolane (100 mg, 0.301 mmol) with 2,5-dichlorobenzyl bromide (93 mg, 0.389 mmol) using cesium hydroxide (70 mg, 0.416 mmol) as described in example 3 followed by chromatography on silica gel (40 % EtOAc in petroleum ether) gave 50 mg (34 %) of the product as white solid, mp 135-140 °C; IR (KBr) 3387, 2959, 1785, 1713, 1650, 1503, 1269  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.78-2.00 (m, 8 H), 3.06-3.23 (m, 2 H), 3.86 (s, 3 H), 4.40 (dt,  $J = 9.0, 6.0$  Hz, 1 H), 4.75-4.81 (m, 1 H), 4.83 (dd,  $J = 18.0, 9.0$  Hz, 2 H), 6.78 (d,  $J = 9.0$  Hz, 1 H), 7.02 (d,  $J = 1.8$  Hz, 1 H), 7.16-7.29 (m, 3 H), 7.38 (d,  $J = 3.6$  Hz, 1 H), 7.54 (d,  $J = 3.6$  Hz, 1 H).

### Example - 23

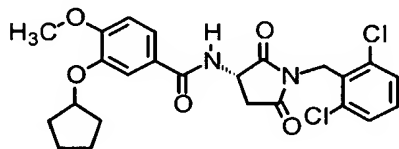
(3*R*)-3-(3-Cyclopentyloxy)-4-methoxyphenylcarboxamido)-1-(2, 5-dichlorobenzyl)-2, 5-dioxo-azolane



The reaction of (3*R*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolane (100 mg, 0.301 mmol) with 2,5-dichlorobenzyl bromide (93 mg, 0.389 mmol) using cesium hydroxide (72 mg, 0.428 mmol) as described in example 3 followed by chromatography on silica gel (40 % EtOAc in petroleum ether) gave 45 mg (30 %) of the product as white solid, mp 135-140 °C; IR (KBr) 3386, 2957, 1785, 1713, 1650, 1505, 1267 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.53-1.98 (m, 8 H), 3.07-3.26 (m, 2 H), 3.88 (s, 3 H), 4.42-4.48 (m, 1 H), 4.76-4.92 (m, 3 H), 6.81-6.86 (m, 2 H), 7.17-7.29 (m, 3 H), 7.42 (s, 1 H), 7.53 (brs, 1 H).

#### Example - 24

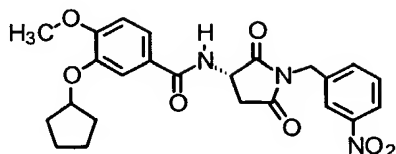
(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(2,5-dichlorobenzyl)-2, 5-dioxoazolane



The reaction of (3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolane (100 mg, 0.301 mmol) with 2,6-dichlorobenzyl bromide (93 mg, 0.389 mmol) using cesium hydroxide (70 mg, 0.416 mmol) as described in example 3 followed by chromatography on silica gel (40 % EtOAc in petroleum ether) gave 40 mg (27 %) of the product as a white solid, mp 204-206 °C; IR (KBr) 3281, 2952, 1783, 1715, 1634, 1505, 1270; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.55- 1.98 (m, 8 H), 2.84 (dd, *J* = 12.0, 9.0 Hz, 1 H), 3.22 (dd, *J* = 18.0, 9.0 Hz, 1 H), 3.87 (s, 3 H), 4.53-4.59 (m, 1 H), 4.78-4.83 (m, 1 H), 5.04 (d, *J* = 3.0 Hz, 2 H), 6.67 (d, *J* = 6.0 Hz, 1 H), 6.81 (d, *J* = 9.0 Hz, 1 H), 7.17-7.35 (m, 5 H); *m/z* (MH<sup>+</sup>, 100 %) 491, 443 (30 %).

#### Example - 25

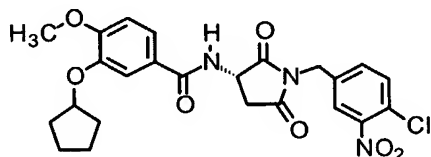
(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-nitrobenzyl)-2, 5-dioxo-azolane



The reaction of (3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxazoline (100 mg, 0.301 mmol) with 3-nitrobenzyl bromide (100 mg, 0.462 mmol) using cesium hydroxide (61 mg, 0.365 mmol) as described in example 3 followed by chromatography on silica gel (30 % EtOAc in petroleum ether) gave 50 mg (35.5 %) of the product as white solid, mp 97-101 °C; IR (KBr) 3391, 2958, 1712, 1652, 1532, 1502, 1348, 1269 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.61-1.99 (m, 8 H), 3.03 (dd, *J* = 18.0, 9.0 Hz, 1 H), 3.17 (dd, *J* = 18.0, 9.0 Hz, 1 H), 3.88 (s, 3 H), 4.40-4.47 (m, 1 H), 4.78-4.81 (m, 1 H), 4.83 (d, *J* = 8.7 Hz, 2 H), 6.76 (d, *J* = 6.6 Hz, 1 H), 6.82 (d, *J* = 8.1, 1 H), 7.26 (d, *J* = 2.0, 1 H), 7.36 (d, *J* = 2.1, 1 H), 7.51 (t, *J* = 8.1, 1 H), 7.76 (d, *J* = 8.1 Hz, 1 H), 8.14 (dd, *J* = 8.1, 3.6 Hz, 1 H), 8.29 (t, *J* = 2.1 Hz, 1 H).

#### 15 **Example -26**

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(4-chloro-3-nitrobenzyl)-2, 5-dioxazoline



20

The reaction of (3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxazoline (100 mg, 0.30 mmol) with 4-chloro-3-nitrobenzyl bromide (90 mg, 0.359 mmol) using cesium hydroxide (61 mg, 0.365 mmol) as described in example 3 followed by chromatography on silica gel (30 % EtOAc in petroleum ether) gave 40 mg (26 %) of the product as white solid, mp 110-112 °C; IR (KBr) 3384, 2957, 1712, 1650, 1537, 1501, 1342, 1269, 1167 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.57-1.64 (m, 4 H), 1.85-2.05 (m, 4 H), 3.05 (dd, *J* = 12.3, 5.7 Hz, 1 H), 3.12 (dd, *J* = 18.0, 9.0 Hz, 1 H), 3.89 (s, 3 H), 4.36-4.43 (m, 1 H), 4.80 (d, *J* = 8.4 Hz, 2 H), 4.83-4.86 (m, 1 H), 6.83 (d, *J* = 5.7 Hz, 1 H), 6.84 (brs, 1 H), 7.24

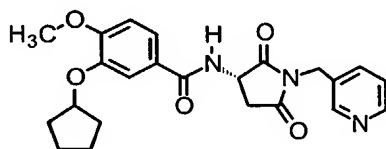
30

(d,  $J = 1.8$  Hz, 1 H), 7.37 (d,  $J = 1.8$  Hz, 1 H), 7.52 (d,  $J = 9.0$  Hz, 1 H), 7.60 (d,  $J = 8.1$  Hz, 1 H), 8.00 (d,  $J = 1.8$  Hz, 1 H).

### Example - 27

5

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-pyridylmethyl)-2,5-dioxo-azolane



10

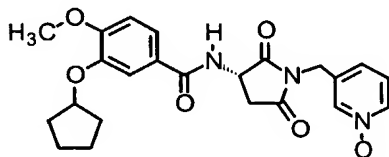
The reaction of (3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxoazolane (100 mg, 0.301 mmol) with 3-picolyl chloride (80 mg, 0.627 mmol) using cesium hydroxide (150 mg, 0.898 mmol) as described in example 3 followed by chromatography on silica gel (30 % EtOAc in petroleum ether) gave 50 mg (39 %) of the product as white solid, mp 85-88 °C; IR (KBr) 3382, 2958, 1710, 1644, 1504, 1400, 1269, 1164  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.80-1.99 (m, 8 H), 2.96 (dd,  $J = 18.0, 6.0$  Hz, 1 H), 3.18 (dd,  $J = 18.0, 6.0$  Hz, 1 H), 3.89 (s, 3 H), 4.43-4.50 (m, 1 H), 4.79 (d,  $J = 3.6$ , 2 H), 4.81-4.83 (m, 1 H), 6.83 (d,  $J = 8.4$  Hz, 1 H), 6.89 (d,  $J = 6.0$  Hz, 1 H), 7.28-7.30 (m, 2 H), 7.35 (d,  $J = 2.1$  Hz, 1 H), 7.79 (dt,  $J = 5.7, 2.1$  Hz, 1 H), 8.54 (dd,  $J = 5.2, 1.8$  Hz, 1 H), 8.67 (d,  $J = 2.1$  Hz, 1 H).

20

### Example - 28

25

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-oxopyridylmethyl)-2,5-dioxoazolane



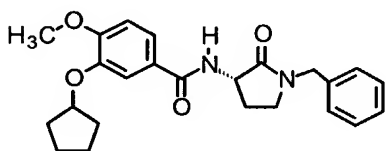
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To a stirred solution of 27 (30 mg, 0.071 mmol) in chloroform (10 ml) was added 50 % *m*-CPBA (70 mg, 0.202 mmol) and the mixture was refluxed for 3 h under stirring. The mixture was cooled to room temperature and diluted with chloroform

(50 ml) and washed with saturated aqueous NaHCO<sub>3</sub> solution. The chloroform solution was washed with water (2 x 50 ml), brine (50 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The crude product obtained after evaporation of the solvent was purified by silica gel column chromatography using 2 % methanol in chloroform to give 20 mg (64 %)  
5 of the product as a white solid, mp 175-180 °C; IR (KBr) 3401, 2957, 1783, 1709, 1638, 1504, 1268 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.79-1.96 (m, 8 H), 3.00 (dd, *J* = 5.7, 12.3 Hz, 1 H), 3.12 (dd, *J* = 18.0, 9.0 Hz, 1 H), 3.89 (s, 3 H), 4.44-4.51 (m, 1 H), 4.71 (d, *J* = 3.6 Hz, 2 H), 4.80-4.85 (m, 1 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 7.23-7.28 (m, 1 H), 7.33-7.41 (m, 3 H), 7.61 (d, *J* = 6.3, 1 H), 8.10 (d, *J* = 6.3 Hz, 1 H), 8.32 (s, 1 H).  
10

### Example -29

(3*S*)-1-Benzyl-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2-oxazolane  
15



Step 1: (3*S*)-3-Amino-1-benzyl-2-oxazolane hydrochloride was prepared by deprotection of (3*S*)-3-(*N*-BOC-Amino-1-benzyl-2-oxazolane (200 mg, 0.687 mmol) using 15 % HCl in ethyl acetate (5 ml) at RT for 4 h.  
20

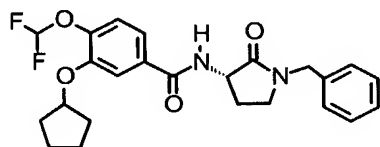
Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-methoxybenzoic acid (165 mg, 0.699 mmol) using oxalyl chloride (113 mg, 1.041 mmol) in dry benzene (5 ml) catalysed by DMF at RT.

25 Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (500 mg, 4.950 mmol) in dry DCM (20 ml) at 0 °C. The crude product obtained was purified by silica gel column chromatography using 4 % methanol in chloroform to give 98 mg of the product as off-white solid, mp 70-75 °C; IR (KBr) 3316, 2956, 1683, 1641, 1505, 1265, 1227 cm<sup>-1</sup>; <sup>1</sup>H NMR  
30 (300 MHz, CDCl<sub>3</sub>) δ 1.59-2.02 (m, 8 H), 2.80-2.89 (m, 1 H), 3.25-3.34 (m, 2 H), 3.89 (s, 3 H), 4.49-4.57 (m, 3 H), 4.83-4.86 (m, 1 H), 6.74 (d, *J* = 8.4, 1 H), 6.84 (d, *J* = 8.4 Hz, 1 H), 7.24-7.42 (m, 7 H ).

**Example -30**

(3*S*)-1-Benzyl-3-(3-cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2-oxoazolane

5



Step 1: (3*S*)-3-Amino-1-benzyl-2-oxoazolane hydrochloride was prepared by deprotection of (3*S*)-3-(*N*-BOC-Amino-1-benzyl-2-oxoazolane (200 mg, 0.687 mmol) using 15 % HCl in ethyl acetate (5 ml) at RT for 4 h.

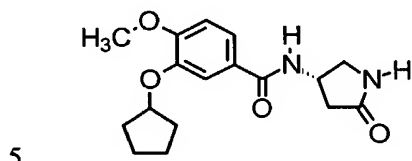
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Step 2: 3-Cyclopentyloxy-4-difluoromethoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-difluoromethoxybenzoic acid (187 mg, 0.686 mmol) using oxalyl chloride (119 mg, 1.096 mmol) in dry benzene (5 ml) catalysed by DMF at RT.

15

Step 3: Coupling Reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (500 mg, 4.950 mmol) in dry DCM (20 ml) at 0 °C. The crude product obtained was purified by silica gel column chromatography using 4 % methanol in chloroform to give 55 mg (y %) of the product as off-white solid, mp 102-103 °C; IR (KBr) 3318, 2900, 1683, 1641, 1500, 1229, 1227 cm<sup>-1</sup>, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.59-1.98 (m, 8 H), 2.76-2.86 (m, 1 H), 3.25-3.32 (m, 2 H), 4.49-4.57 (m, 3 H), 4.85-4.89 (m, 1 H), 6.57 (t, *J* = 71.7 Hz, 1 H), 6.89 (d, *J* = 3.6 Hz, 1 H), 7.14 (d, *J* = 8.4, 1 H), 7.22-7.37 (m, 6 H), 7.48 (d, *J* = 1.8 Hz, 1 H)

20  
25

**Example -31**(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-5-oxoazolane

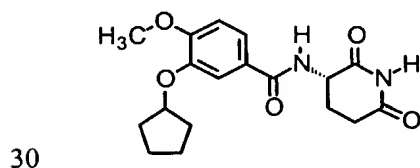
Step 1: (3*S*)-3-Amino-5-oxoazolane hydrochloride was prepared by deprotection of (3*S*)-3-(*N*-BOC-Amino)-5-oxoazolane (60 mg, 0.299 mmol) using 15 % HCl in ethyl acetate (5 ml) at RT for 4 h.

10

Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-methoxybenzoic acid (71 mg, 0.300 mmol) using oxalyl chloride (42 mg, 0.387 mmol) in dry benzene (3 ml) catalysed by DMF at RT.

15 Step 3: Coupling Reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (200 mg, 1.980 mmol) in dry DCM (10 ml) at 0 °C. The crude product obtained was purified by silica gel column chromatography using 4 % methanol in chloroform to give 20 mg of the product as off-white solid, mp 103-105 °C; IR (KBr) 3303, 2954, 1770, 1688, 1509, 1269, 1022 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.61-1.98 (m, 8 H), 2.34 (dd, *J* = 17.1, 3.9 Hz, 1 H), 2.78 (dd, *J* = 17.1, 8.4 Hz, 1 H), 3.35 (dd, *J* = 10.2, 3.0 Hz, 1 H), 3.80 (dd, *J* = 10.2, 6.3 Hz, 1 H), 3.87 (s, 3 H), 4.80-4.85 (m, 2 H), 5.99 (brs, 1 H), 6.81 (brs, 1 H) 6.82 (d, *J* = 8.4 Hz, 1 H), 7.29 (dd, *J* = 8.1, 2.1 Hz, 1 H), 7.41 (d, *J* = 2.4 Hz, 1 H).

20

25 **Example - 32**(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,6-dioxohexahydropyridine

Step 1: (3*S*)-3-Aminohexahydro-2,6-pyridinedione was prepared as follows: To a stirred solution of (3*S*)-3-(*N*-Cbz-Amino)hexahydro-2,6-pyridinedione (200 mg, 0.76 mmol) in ethanol (10 ml) was added 5 % Pd/C (10 mg) and the mixture was stirred under hydrogen atmosphere for 1 h. The reaction mixture was filtered  
5 through a celite bed and the filtrate was evaporated to give free amine quantitatively yield as a greenish yellow viscous liquid which was used as such for coupling reaction.

Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared as follows:  
10 To a well stirred solution of 3-Cyclopentyloxy-4-methoxybenzoic acid (200 mg, 0.847 mmol) in dry benzene (3 ml) was added oxalyl chloride (140 mg, 1.1 mmol) at RT. The reaction was initiated with a drop of dry DMF and stirred at RT for 1 h under nitrogen atmosphere. The solvent was removed under reduced pressure to give the acid chloride quantitatively as a viscous residue, which was used as such  
15 for the coupling reaction.

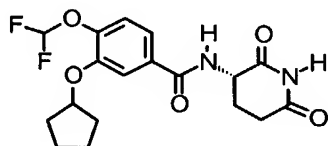
Step 3: Coupling reaction: The acid chloride (step 2) dissolved in dry dichloromethane (5 ml) was added to a stirred and cooled (0 °C) solution of the crude amine (step 1) and triethylamine (200 mg, 1.98 mmol) in dry  
20 dichloromethane (5 ml). The mixture was stirred at RT for 1 h. The mixture was diluted with dichloromethane (100 ml) and washed with water (3 x 100 ml), brine (50 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The crude product obtained after evaporation of the solvent was purified by silica gel column chromatography using 30 % EtOAc in chloroform as eluent to give 110 mg ( 58 %) of the product as white solid, mp  
25 117-120 °C; IR (KBr) 3257, 2957, 1713, 1639, 1421, 1267, 990 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.59-2.04 (m, 9 H), 2.70-2.87 (m, 3 H), 3.88 (s, 3 H), 4.68-4.75 (m, 1 H), 4.81-4.86 (m, 1 H), 6.84 (d, *J* = 9.0 Hz, 1 H), 6.90 (d, *J* = 6.2 Hz, 1 H), 7.32 (d, *J* = 12.0 Hz, 1 H), 7.40 (d, *J* = 3.2 Hz, 1 H), 8.17 (s, 1 H).



**Example - 33**

(3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2,6-dioxohexahydro-pyridine

5



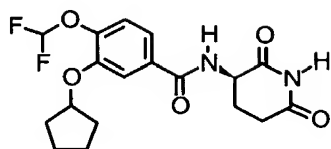
Step 1: (3*S*)-3-Aminohexahydro-2,6-pyridinedione was prepared by deprotection of (3*S*)-3-(*N*-Cbz-Amino)hexahydro-2,6-pyridinedione (300 mg, 1.14 mmol) with  
10 5 % Pd/C (30 mg) in EtOH (10 ml).

Step 2: 3-Cyclopentyloxy-4-difluoromethoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-difluoromethoxybenzoic acid (312 mg, 1.14 mmol) and oxalyl chloride (219 mg, 1.72 mmol) in dry benzene (10 ml) catalyzed by dry  
15 DMF at RT.

Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (288 mg, 2.85 mmol) in dry dichloromethane (5 ml) at RT for 1 h. The crude product was purified by silica gel column chromatography  
20 using 30 % ethyl acetate in chloroform to give 160 mg (x %) of the product as white solid, mp 149-152 °C; IR ( KBr ) 3382, 3212, 2967, 1765, 1661, 1501, 1361, 1200, 1112, 989 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.60-2.02 (m, 10 H), 2.64-2.73 (m, 1 H), 2.79-2.84 (m, 1 H), 4.72-4.81(m, 1 H), 4.84-4.88 (m, 1 H), 6.56 (t, *J* = 74.7 Hz, 1 H), 7.02 (d, *J* = 5.7 Hz, 1 H), 7.13 (d, *J* = 8.1 Hz, 1 H), 7.27  
25 (d, *J* = 2.1 Hz, 1 H), 7.47 (s, 1 H), 8.40 (s, 1 H).

**Example - 34**

(3*R*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2,6-dioxohexahydro-pyridine  
30



Step 1: (3*R*)-3-Aminohexahydro-2,6-pyridinedione was prepared by deprotection of (3*R*)-3-(*N*-Cbz-Amino)hexahydro-2,6-pyridinedione (300 mg, 1.14 mmol) with  
5 5 % Pd/C (15 mg) in ethanol (10 ml).

Step 2: 3-Cyclopentyloxy-4-difluoromethoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-methoxybenzoic acid (312 mg, 1.14 mmol) using oxalyl chloride (219 mg, 1.72 mmol) in dry benzene (10 ml) catalysed by DMF at RT.

10

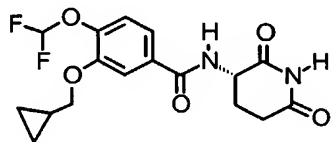
Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (288 mg, 2.85 mmol) in dry dichloromethane (10 ml). The crude product was purified by silica gel column chromatography using 30 % ethyl acetate in chloroform as eluent to give 300 mg of the product as white solid,  
15 mp 149-152 °C; IR (KBr) 3382, 3212, 1962, 1705, 1661, 1543, 1501, 1361, 1271, 1200, 1112, 989 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.64-2.05 (m, 9 H), 2.64-2.73 (m, 1 H), 2.79-2.85 (m, 2 H), 4.72-4.80 (m, 1 H), 4.84-4.88 (m, 1 H), 6.56 (t, *J* = 74.7 Hz, 1 H), 7.02 (d, *J* = 5.7 Hz, 1 H), 7.13 (d, *J* = 8.1 Hz, 1 H), 7.26 (d, *J* = 2.1 Hz, 1 H), 7.47 (d, *J* = 2.1 Hz, 1 H), 8.40 (brs, 1 H).

20

### **Example - 35**

(3*S*)-3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenylcarboxamido)-2,6-dioxo-hexahydropyridine

25



Step 1: (3*S*)-3-Aminohexahydro-2,6-pyridinedione was prepared by deprotection of (3*S*)-3-(*N*-Cbz-Amino)hexahydro-2,6-pyridinedione (305 mg, 1.16 mmol)  
30 using 5 % Pd/C (15 mg) in ethanol (10 ml).

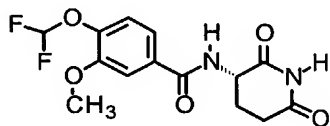
Step 2: 3-Cyclopropylmethyloxy-4-difluoromethoxybenzoyl chloride was prepared from 3-Cyclopropylmethyloxy-4-difluoromethoxybenzoic acid (200 mg, 0.77 mmol) using oxalyl chloride (150 mg, 1.18 mmol) in dry benzene (10 ml) catalysed by DMF at RT.

5

Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (294 mg, 2.91 mmol) in dry dichloromethane (10 ml). The crude product was purified by silica gel column chromatography using 30 % ethyl acetate in chloroform as eluent to give 150 mg of the product as white solid,  
10 mp 149-151 °C; IR (KBr) 3293, 2909, 1717, 1640, 1539, 1507, 1270, 1198, 1001, 761  $\text{cm}^{-1}$ ; IR (KBr) 3293, 3092, 1717, 1640, 1539, 1507, 1198, 1139, 1001, 761  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.38 (d,  $J = 4.5$  Hz, 2 H), 0.36 (d,  $J = 7.2$  Hz, 2 H), 1.26-1.30 (m, 1 H), 2.05-2.21 (m, 1 H), 2.51-2.57 (m, 1 H), 2.79-2.81 (m, 2 H), 3.87 (d,  $J = 7.2$  Hz, 2 H), 4.87-4.95 (m, 1 H), 6.65 (t,  $J = 74.7$  Hz, 1 H),  
15 7.06 (d,  $J = 8.1$  Hz, 1 H), 7.25-7.30 (m, 2 H), 7.39 (s, 1 H), 9.27 (s, 1 H).

### Example - 36

20 (3*S*)-3-(4-Difluoromethoxy-3-methoxyphenylcarboxamido)-2,6-dioxohexahydro-pyridine



Step 1: (3*S*)-3-Aminohexahydro-2,6-pyridinedione was prepared by deprotection  
25 of (3*S*)-3-(*N*-Cbz-Amino)hexahydro-2,6-pyridinedione (250 mg, 0.95 mmol) using 5 % Pd/C (25 mg) in ethanol (10 ml).

Step 2: 4-Difluoromethoxy-3-methoxybenzoyl chloride was prepared from 4-difluoro-methoxy-3-methoxy benzoic acid (210 mg, 0.96 mmol) using oxalyl  
30 chloride (185 mg, 1.45 mmol) in dry benzene (10 ml) catalysed by DMF at RT.

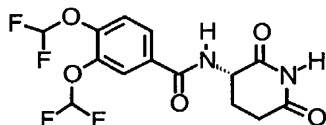
Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (243 mg, 2.40 mmol) in dry dichloromethane (10 ml).

The crude product was purified by silica gel column chromatography using 30 % ethyl acetate in chloroform as eluent to give 130 mg of the product as white solid, mp 150-152 °C; IR (KBr) 3286, 3100, 1712, 1650, 1543, 1510, 1375, 1268, 1190, 1129, 1028, 763 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.19-2.04 (m, 1 H), 2.65-2.73 (m, 1 H), 2.83 (s, 2 H), 3.92 (s, 3 H), 4.74-4.83 (m, 1 H), 6.58 (t, *J* = 74.4 Hz, 1 H), 7.07 (s, 1 H), 7.14 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1 H), 7.47 (s, 1 H), 8.48 (s, 1 H).

### Example - 37

10

(3*S*)-3-[3,4-Di(difluoromethoxy)phenylcarboxamido]-2,6-dioxohexahydropyridine



15 Step 1: (3*S*)-3-Aminohexahydro-2,6-pyridinedione was prepared by deprotection of (3*S*)-3-(*N*-Cbz-Amino)hexahydro-2,6-pyridinedione (660 mg, 2.52 mmol) using 5 % Pd/C (50 mg) in EtOH (25 ml).

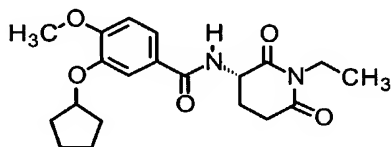
Step 2: 3,4-Di(difluoromethoxy)benzoyl chloride was prepared from 3,4-Di(difluoromethoxy)-benzoic acid (600 mg, 2.36 mmol) using oxalyl chloride (450 mg, 3.54 mmol) in benzene (20 ml) catalysed by dry DMF at RT.

Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (636 mg, 6.29 mmol) in dry dichloromethane (20 ml).  
 25 The crude product was purified by silica gel column chromatography using 40-50 % ethyl acetate in chloroform as eluent to give 500 mg of the product as white solid, mp 99-103 °C; IR (KBr) 3381, 2216, 3100, 1710, 1658, 1546, 1507, 1363, 1260, 1148, 1050, 758 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD) δ 2.14-2.23 (m, 2 H), 2.65-2.89 (m, 2 H), 4.81-4.87 (m, 1 H), 6.86 (t, *J* = 72.9 Hz, 1 H), 6.93 (t, *J* = 72.9 Hz, 1 H), 7.38 (d, *J* = 9.0 Hz, 1 H), 7.77 (d, *J* = 9.0 Hz, 1 H), 7.79 (s, 1 H).  
 30

**Example - 38**

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-ethyl-2,6-dioxohexahydro-pyridine

5



Step 1: (3*S*)-3-Amino-1-ethylhexahydro-2,6-pyridinedione was prepared by deprotection of (3*S*)-3-(*N*-Cbz-Amino)-1-ethylhexahydro-2,6-pyridinedione (200 mg, 0.68 mmol) using 5 % Pd/C (20 mg) in ethanol (10 ml) at RT for 1 h.

10

Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-methoxybenzoic acid (170 mg, 0.72 mmol) using oxalyl chloride (140 mg, 1.1 mmol) in dry benzene (5 ml) catalysed by DMF at RT.

15

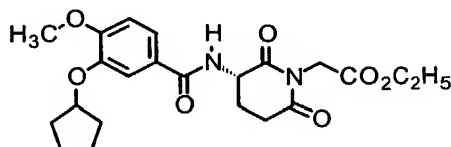
Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (172 mg, 1.70 mmol) in dry dichloromethane (10 ml). The crude product was purified by silica gel column chromatography using 30 % ethyl acetate in petroleum ether as eluent to give 100 mg ( 58 %) of the product as white solid, mp 68-70 °C; IR (KBr) 3352, 2962, 1679, 1640, 1414, 1267, 991 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.15 (t, *J* = 6.9 Hz, 3 H ), 1.59-2.00 (m, 9 H), 2.66-2.94 (m, 1 H), 3.78-3.93 (m, 5 H), 4.60-4.68 (m, 1 H), 4.81-4.87 (m, 1 H), 6.85 (d, *J* = 9.0 Hz, 1 H), 7.01 (d, *J* = 3.0 Hz, 1 H), 7.33 (dd, *J* = 9.0, 2.1 Hz, 1 H), 7.45 (s, 5 H).

20

**Example - 39**

Ethyl 2-[(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,6-dioxohexahydro-1-pyridinyl]acetate

25



Step 1: Ethyl 2-[(3*S*)-3-Amino-2,6-dioxohexahydro-1-pyridinyl]acetate was prepared by deprotection (3*S*)-3-(*N*-Cbz-Amino)hexahydro-2,6-pyridinedione (250 mg, 0.71 mmol) using 5 % Pd/C (10 mg) in ethanol (10 ml) at RT for 1 h.

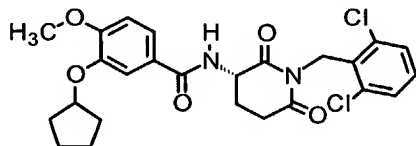
- 5 Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared from 3-cyclopentyloxy-4-methoxybenzoic acid (170 mg, 0.72 mmol) using oxalyl chloride (138 mg, 1.08 mmol) in dry benzene (5 ml) catalysed DMF at RT.

- Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride  
10 (step 2) using triethylamine (180 mg, 1.78 mmol) in dry dichloromethane (5 ml). The crude product was purified by silica gel column chromatography using 25 % ethyl acetate in petroleum ether as eluent to give 200 mg of the product as off-white solid, mp 184-186 °C; IR (KBr) 3232, 2965, 1732, 1632, 1512, 1333, 1173 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.28 (t, *J* = 6.7 Hz, 3 H), 1.64-2.04 (m, 9 H),  
15 2.69-2.96 (m, 3 H), 3.88 (s, 3 H), 4.19 (q, *J* = 8.6 Hz, 2 H), 4.75-4.86 (m, 2 H), 6.85 (d, *J* = 9.0 Hz, 1 H), 6.93 (d, *J* = 3.0 Hz, 1 H), 7.32 (d, *J* = 9.0 Hz, 1 H), 7.39 (s, 1 H).

**Example - 40**

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(2,6-dichlorobenzyl)-2,6-dioxo-hexahydropyridine

5



Step 1: (3*S*)-3-Amino)-1-(2,6-dichlorobenzyl)hexahydro-2,6-pyridinedione was prepared by deprotection (3*S*)-3-(*N*-Cbz-amino)-1-(2,6-dichlorobenzyl)hexahydro-2,6-pyridinedione (200 mg, 0.45 mmol) using 5 % Pd/C (10 mg) in ethanol (10 ml) at RT for 1 h

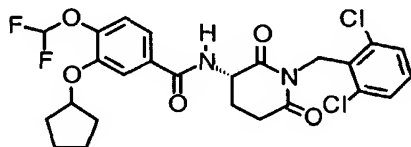
Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-methoxybenzoic acid (132mg, 0.56 mmol) using oxalyl chloride (160 mg, 0.83 mmol) in dry benzene (5 ml) catalysed DMF at RT.

Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (115 mg, 1.13 mmol) in dry dichloromethane (5 ml). The crude product was purified by silica gel column chromatography using 30 % ethyl acetate in petether as eluent to give 60 mg of the product as white solid, mp 156-158 °C; IR (KBr) 3227, 2964, 1737, 1692, 1641, 1503, 1332, 1262, 1167, 999, 779 cm<sup>-1</sup>.; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.54-1.98 (m, 9 H), 2.63-2.74 (m, 1 H), 2.84-2.92 (m, 2 H), 3.87 (s, 3 H), 4.63-4.72 (m, 1 H), 4.83 (d, *J* = 3 Hz, 1 H), 5.26 (dd, *J* = 14.7, 7.5 Hz, 2 H), 6.82 (d, *J* = 8.7 Hz, 1 H), 6.94 (d, *J* = 4.8 Hz, 1 H), 7.14 (d, *J* = 7.2 Hz, 1 H), 7.26 -7.30 (m, 3 H), 7.37 (s, 1 H).

**Example - 41**

(3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-1-(2,6-dichloro-benzyl)-2,6-dioxohexahydropyridine

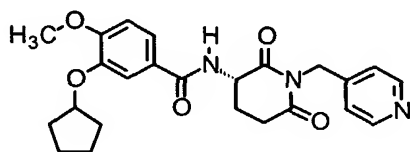
5



A mixture of (3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2,6-dioxo-hexahydropyridine (200 mg, 0.52 mmol), 2-bromomethyl-1,3-dichlorobenzene (190 mg, 0.79 mmol), potassium carbonate (130 mg, 30.94 mmol) and tetrabutylammonium iodide (20 mg, 0.05 mmol) in dry acetone (10 ml) was stirred at RT for 48 h under nitrogen. The reaction mixture was filtered through a celite bed and the filtrate was diluted with ethyl acetate (100 ml) and washed with water (3 x 100 ml) followed by brine (50 ml) and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product obtained after evaporation of the solvent was purified by silica gel column chromatography using 30 % ethyl acetate in petroleum ether as eluent to give 160 mg of the product as white solid, mp 78-90 °C; IR (KBr) 3356, 2964, 1736, 1689, 1542, 1500, 1334, 1169, 1116, 999, 767 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.59-1.98 (m, 9 H), 2.67-2.75 (m, 1 H), 2.80-2.98 (m, 2H), 4.65-4.72 (m, 1 H), 4.85-4.90 (m, 1 H), 5.27 (dd, *J* = 14.7, 6.6 Hz, 2 H), 6.57 (t, *J* = 74.7 Hz, 1 H), 7.01 (s, 1 H), 7.12-1.17 (m, 2 H), 7.22-7.30 (m, 3 H), 7.46 (s, 1 H).

**Example - 42**

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,6-dioxo-1-(4-pyridylmethyl)-hexahydropyridine



Step 1: (3*S*)-3-Amino-1-(4-pyridylmethyl)hexahydro-2,6-pyridinedione was prepared by deprotection of (3*S*)-3-(*N*-Cbz-Amino)hexahydro-2,6-pyridinedione (250 mg, 0.70 mmol) using 5 % Pd/C (20 mg) in EtOH (6 ml) at RT for 1 h.

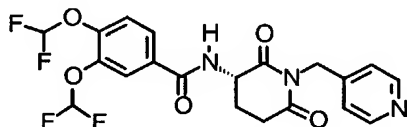


Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-methoxybenzoic acid (170 mg, 0.72 mmol) using oxalyl chloride (162 mg, 1.275 mmol) in dry benzene (5 ml) catalysed DMF at RT for 1 h.

Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (177 mg, 1.75 mmol) in dry dichloromethane (5 ml). The crude product was purified by silica gel column chromatography using 4 % methanol in chloroform as eluent to give 70 mg of the product as white solid, mp 185-187 °C; IR (KBr) 3435, 2955, 1654, 1505, 1421, 1337, 1166  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.61-1.98 (m, 9 H), 2.69-3.00 (m, 3 H), 3.88 (s, 3 H), 4.71-4.84 (m, 2 H), 4.89-5.03 (m, 2 H), 6.84 (d,  $J = 9.0$  Hz, 1 H), 7.01 (d,  $J = 6.0$  Hz, 2 H), 7.32 (dd,  $J = 12, 1.8$  Hz, 1 H), 7.40 (s, 1 H), 8.52 (d,  $J = 6.0$  Hz, 2 H).

#### Example - 43

(3*S*)-3-[3,4-Di(di fluoromethoxy)phenylcarboxamido]-1-(4-pyridylmethyl)-2,6-dioxo-hexahydropyridine



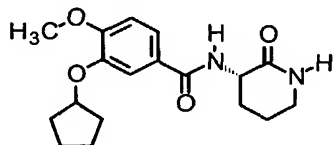
A mixture of (3*S*)-3-[3,4-Di(di fluoromethoxy)phenylcarboxamido]-2,6-dioxohexa-hydropyridine (150 mg, 0.41 mmol), 4-picolyl chloride hydrochloride (100 mg, 0.61 mmol), potassium carbonate (170 mg, 1.23 mmol) and tetrabutylammonium iodide (15 mg, 0.04 mmol) in dry acetone (10 ml) was stirred at RT for 72 h under nitrogen. The reaction mixture was filtered through celite bed and the filtrate was diluted with ethyl acetate (100 ml) and washed with water (3 x 100 ml) followed by brine (50 ml) and dried ( $\text{Na}_2\text{SO}_4$ ). The crude product obtained after evaporation of the solvent was purified by silica gel column chromatography using 3 % methanol in chloroform as eluent to give 100 mg of the product as white solid; IR (KBr) 3391, 3039, 1733, 1678, 1654, 1508, 1277, 1167, 1109, 1045, 1001  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  2.20-2.32 (m, 2

H), 2.90-2.98 (m, 2 H), 4.88-4.99 (m, 3 H), 6.85 (t,  $J = 73.2$  Hz, 1 H), 6.93 (t,  $J = 72.9$  Hz, 1 H), 7.33-7.39 (m, 3 H), 7.76-7.79 (m, 2 H), 8.14-8.43 (m, 2 H).

#### **Example - 44**

5

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2-oxohexahydropyridine



- 10 Step 1: (3*S*)-3-Amino-2-oxohexahydropyridine hydrochloride was prepared as follows: (3*S*)-3-(*N*-BOC-Amino)-2-oxohexahydropyridine (300 mg, 1.40 mmol) was added to a well-stirred and cooled (0 °C) solution of 15 % hydrochloric acid in ethyl acetate (10 ml) under nitrogen atmosphere. The temperature of the mixture was raised to RT and was stirred at the same temperature for 3 h. The
- 15 solvent and excess acid was evaporated under reduced pressure to give the amine hydrochloride as white solid which was used as such for the coupling reaction.

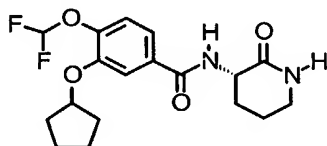
- Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-methoxybenzoic acid (200 mg, 0.84 mmol) using oxalyl chloride (162 mg, 1.27 mmol) in dry benzene (5 ml) catalysed by DMF at RT.
- 20

- Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (257 mg, 2.54 mmol) in dry dichloromethane (10 ml). The crude product was purified by silica gel column chromatography using 2 %
- 25 methanol in chloroform as eluent to give 140 mg of the product as white solid, mp 172-174 °C; IR (KBr) 3327, 3220, 2948, 1690, 1631, 1537, 1508, 1270, 1228, 1139, 1014, 762  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.56-2.04 (m, 11 H), 2.69-2.78 (m, 1 H), 3.37-3.42 (m, 2 H), 3.87 (s, 3 H), 4.40 (quint,  $J = 5.7$  Hz, 1 H), 4.84 (hept,  $J = 3.6$  Hz, 1 H), 5.89 (brs, 1 H), 6.83 (d,  $J = 8.4$  Hz, 1 H), 7.07 (brs, 1
- 30 H), 7.32 (d,  $J = 8.4$  Hz, 1 H), 7.40 (s, 1 H).

**Example - 45**

(3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2-oxohexahydropyridine

5



Step 1: (3*S*)-3-Amino-2-oxohexahydropyridine hydrochloride was prepared by deprotection of (3*S*)-3-(*N*-BOC-Amino)-2-oxohexahydropyridine (236 mg, 1.10 mmol) using 15 % hydrochloric acid in ethyl acetate (10 ml) for 3 h.

10

Step 2: 3-Cyclopentyloxy-4-difluoromethoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-difluoromethoxybenzoic acid (x mg, y mmol) using oxalyl chloride (105 mg, 0.82 mmol) in dry benzene (5 ml) catalysed by DMF at RT for 1 h.

15

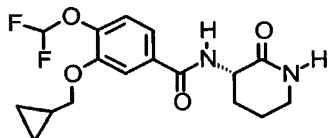
Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (200 mg, 1.98 mmol) in dry dichloromethane (5 ml). The crude product was purified by silica gel column chromatography using 2 % methanol in chloroform as eluent to give 70 mg of the product as white solid, mp 59-64 °C; IR (KBr) 3301, 2958, 1661, 1502, 1271, 1115, 1048, 759 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.65-2.00 (m, 11 H), 2.68-2.72 (m, 1 H), 3.38-3.42 (m, 2 H), 4.39 (quint, *J* = 5.1 Hz, 1 H), 4.86-4.88 (m, 1 H), 5.96 (brs, 1 H), 6.56 (t, *J* = 74.7 Hz, 1 H), 7.13 (d, *J* = 8.1 Hz, 1 H), 7.25-7.28 (m, 2 H), 7.48 (s, 1 H).

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**Example - 46**

(3*S*)-3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenylcarboxamido)-2-oxohexahydro-pyridine

5



Step 1: (3*S*)-3-Amino-2-oxohexahydropyridine hydrochloride was prepared by deprotection of (3*S*)-3-(*N*-BOC-Amino)-2-oxohexahydropyridine (321 mg, 1.50 mmol) using 15 % hydrochloric acid in ethyl acetate (10 ml) for 3 h.

10

Step 2: 3-Cyclopropylmethoxy-4-difluoromethoxybenzoyl chloride was prepared from 3-Cyclopropylmethoxy-4-difluoromethoxybenzoic acid (258 mg, 1.00 mmol) using oxalyl chloride (191 mg, 1.50 mmol) in dry benzene (5 ml) catalysed by DMF at RT for 1 h.

15

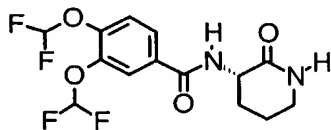
Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (202 mg, 2.00 mmol) in dry dichloromethane (10 ml). The crude product was purified by silica gel column chromatography using 2 % methanol in chloroform as eluent to give 140 mg of the product as white solid, mp 52-60 °C; IR (KBr) 3297, 1876, 1651, 1504, 1271, 1207, 1116, 1006, 759 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.33-0.38 (m, 2 H), 0.61-0.67 (m, 2 H), 1.24-1.31 (m, 1 H), 1.58-1.72 (m, 1 H), 1.95-2.04 (m, 2 H), 2.63-2.72 (m, 1 H), 3.37-3.41 (m, 2 H), 3.90 (d, *J* = 6.9 Hz, 2 H), 4.38 (quint, *J* = 5.4 Hz, 1 H), 5.92 (brs, 1 H), 6.66 (t, *J* = 75.0 Hz, 1 H), 7.13 (d, *J* = 8.4 Hz, 1 H), 7.24-7.30 (m, 2 H), 7.43 (s, 1 H).

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**Example - 47**(3*S*)-3-[3,4-Di(di fluoromethoxy)phenylcarboxamido]-2-oxohexahydropyridine

5



Step 1: (3*S*)-3-Amino-2-oxohexahydropyridine hydrochloride was prepared by deprotection of (3*S*)-3-(*N*-BOC-Amino)-2-oxohexahydropyridine (200 mg, 0.93 mmol) using 15 % hydrochloric acid in ethyl acetate (10 ml) for 3 h.

10

Step 2: 3,4-Di(di fluoromethoxy)benzoyl chloride was prepared from 3,4-Di(di fluoromethoxy)-benzoic acid (150 mg, 0.59 mmol) using oxalyl chloride (115 mg, 0.90 mmol) in dry benzene (5 ml) catalysed by DMF at RT for 1 h.

15

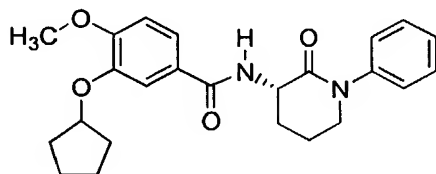
Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (180 mg, 1.78 mmol) in dry dichloromethane (10 ml). The crude product was purified by silica gel column chromatography using 1-2 % methanol in chloroform as eluent to give 100 mg of the product as white solid, mp 144-146 °C; IR (KBr) 3247, 2957, 1657, 1508, 1274, 1134, 1054, 793 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.59-1.70 (m, 2 H), 1.91-2.19 (m, 2 H), 2.61-2.79 (m, 1 H), 3.34-3.41 (m, 2 H), 4.35-4.43 (m, 1 H), 5.86 (brs, 1 H), 6.55 (t, *J* = 72.9 Hz, 1 H), 7.24 (d, *J* = 8.1 Hz, 1 H), 7.33 (brs, 1 H), 7.62 (d, *J* = 8.4 Hz, 1 H), 7.7 (s, 1 H).

20

25

**Example - 48**(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2-oxo-1-phenylhexahydro-pyridine

30



Step 1: (3*S*)-3-Amino-2-oxo-1-phenylhexahydropyridine hydrochloride was prepared by deprotection of (3*S*)-3-(*N*-BOC-Amino)-2-oxo-1-phenylhexahydropyridine (250 mg, 0.89 mmol) using 15 % hydrochloric acid in ethyl acetate (10 ml) for 3 h.

5

Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-methoxybenzoic acid (200 mg, 0.84 mmol) using oxalyl chloride (160 mg, 1.26 mmol) in dry benzene (5 ml) catalysed by DMF at RT for 1 h.

10

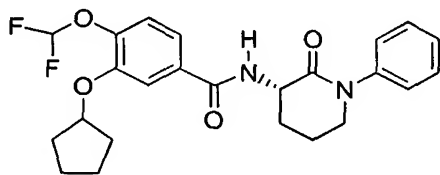
Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (260 mg, 2.57 mmol) in dry dichloromethane (5 ml). The crude product was purified by silica gel column chromatography using 1-2 % methanol in chloroform as eluent to give 90 mg of the product as a white solid, mp 58-60 °C; IR (KBr) 3337, 2954, 1640, 1503, 1266, 1224, 1024, 761 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.57-1.98 (m, 9 H), 2.09-2.17 (m, 2 H), 2.85-2.91 (m, 1 H), 3.76 (t, *J* = 6.3 Hz, 2 H), 3.86 (t, 3 H), 4.56-4.64 (m, 1 H), 4.80-4.85 (m, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 7.23-7.42 (m, 8 H).

20

#### **Example - 49**

(3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2-oxo-1-phenyl-hexahydropyridine

25



Step 1: (3*S*)-3-Amino-2-oxo-1-phenylhexahydropyridine hydrochloride was prepared by the deprotection of (3*S*)-3-(*N*-BOC-Amino)-2-oxo-1-phenylhexahydropyridine (200 mg, 0.72 mmol) using 15 % HCl in EtOAc (10 ml) at RT for 2 h.

30

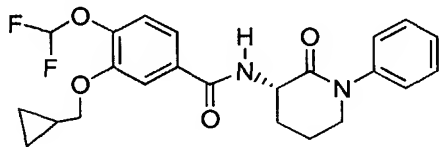
Step 2: 3-Cyclopentyloxy-4-difluoromethoxybenzoyl chloride was prepared from 3-Cyclopropyloxy-4-difluoromethoxybenzoic acid (180 mg, 0.66 mmol) using

oxalyl chloride (126 mg, 0.99 mmol) in dry benzene (5 ml) catalysed by DMF at RT for 1 h

- Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (200 mg, 1.98 mmol) in dry dichloromethane (5 ml). The crude product was purified by silica gel column chromatography using 20 % EtOAc in chloroform to give 80 mg of the product as a white solid, mp 49-51 °C; IR (KBr) 3317, 2957, 1639, 1545, 1497, 1271, 1201, 1115, 1043, 761  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.64-1.89 (m, 9 H), 2.10-2.46 (m, 2 H), 2.82-2.90 (m, 1 H), 3.77 (t,  $J = 5.7$  Hz, 2 H), 4.56-4.63 (m, 1 H), 4.87 (brs, 1H), 6.50 (t,  $J = 75.0$  Hz, 1 H), 7.13 (d,  $J = 8.0$  Hz, 1 H), 7.24-7.47 (m, 7 H).

### **Example - 50**

- (3*S*)-3-(3-Cyclopropylmethyloxy-4-difluoromethoxyphenylcarboxamido)-2-oxo-1-phenyl-hexahydropyridine

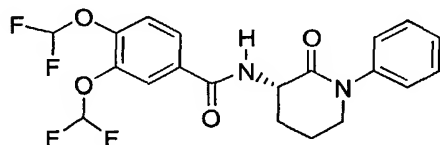


- Step 1: (3*S*)-3-Amino-2-oxo-1-phenylhexahydropyridine hydrochloride was prepared by the deprotection of (3*S*)-3-(*N*-BOC-Amino)-2-oxo-1-phenylhexahydropyridine (200 mg, 0.72 mmol) using 15 % HCl in EtOAc (10 ml) at RT for 3 h.
- Step 2: 3-Cyclopropylmethyloxy-4-difluoromethoxybenzoyl chloride was prepared from 3-Cyclopropylmethyloxy-4-difluoromethoxybenzoic acid (190 mg, 0.73 mmol) using oxalyl chloride (141 mg, 1.11 mmol) in dry benzene (5 ml) catalysed by DMF at RT for 1 h.
- Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (250 mg, 2.47 mmol) in dry dichloromethane (5 ml). The crude product was purified by silica gel column chromatography using 20 % EtOAc in chloroform as eluent to give 50 mg of the product as white solid, mp 47-

55 °C; IR (KBr) 3314, 2945, 1639, 1596, 1503, 1427, 1271, 1116, 1025, 762 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.32-0.37 (m, 2 H), 0.60-0.67 (m, 2 H), 1.24-1.30 (m, 1 H), 1.69-1.77 (m, 1 H), 2.08-2.15 (m, 2 H), 2.78-2.85 (m, 1 H), 3.75 (t, *J* = 6.3 Hz, 2 H), 3.88 (d, *J* = 6.9 Hz, 2 H), 4.55-4.63 (m, 1 H), 6.64 (t, *J* = 75.3 Hz, 1 H), 7.13 (dd, *J* = 5.4, 3.0 Hz, 1 H), 7.23-7.42 (m, 8 H).

### Example - 51

(3*S*)-3-[3,4-Di(di fluoromethoxy)phenylcarboxamido]-2-oxo-1-phenylhexahydropyridine



Step 1: (3*S*)-Amino-2-oxo-1-phenylhexahydropyridine hydrochloride was prepared by the deprotection of (3*S*)-3-(*N*-BOC-Amino)-2-oxo-1-phenylhexahydropyridine (200 mg, 0.72 mmol) using 15 % HCl in EtOAc (10 ml) at RT for 2 h.

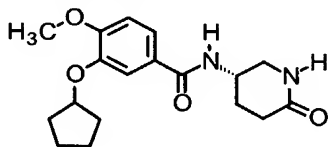
Step 2: 3,4-Di(di fluoromethoxy)benzoyl chloride was prepared from 3,4-Di(di fluoromethoxy)-benzoic acid (160 mg, 0.63 mmol) using oxalyl chloride (120 mg, 0.94 mmol) in dry benzene (5 ml) catalysed by DMF at RT for 1 h.

Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (200 mg, 1.98 mmol) in dry dichloromethane (5 ml). The crude product was purified by silica gel column chromatography using 20-25 % EtOAc in chloroform as eluent to give 50 mg of the product as white solid, mp 41-43 °C; IR (KBr) 3305, 2952, 1639, 1593, 1494, 1277, 1120, 761 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.68-1.82 (m, 1 H), 2.07-2.18 (m, 2 H), 2.73-2.81 (m, 1 H), 3.74-3.78 (m, 2 H), 4.50-4.62 (m, 1 H), 6.54 (t, *J* = 72.6 Hz, 1 H), 6.55 (t, *J* = 72.6 Hz, 1 H), 7.21-7.31 (m, 4 H), 7.38-7.19 (m, 2 H), 7.58-7.73 (m, 3 H).



**Example - 52**

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-6-oxohexahydropyridine



5

Step 1: (3*S*)-3-Amino-6-oxo-1-phenylhexahydropyridine hydrochloride was prepared as follows: (3*S*)-3-(*N*-BOC-Amino)-6-oxohexahydropyridine (150 mg, 0.70 mmol) was added to a stirred and cooled (0 °C) solution of 15 %  
 10 hydrochloric acid in ethyl acetate (5 ml). The mixture was slowly warmed to RT and further stirred at RT for 3 h under nitrogen. Ethyl acetate and excess acid were evaporated under reduced pressure to give the amine hydrochloride as white solid, which was used as such for the coupling reaction.

15 Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared as follows: Oxalyl chloride (130 mg, 1.02 mmol) was added to a well-stirred solution of 3-Cyclopentyloxy-4-methoxybenzoic acid (160 mg, 0.67 mmol) in dry benzene (5 ml) at room temperature under nitrogen atmosphere. The reaction was initiated with a drop of dry DMF and stirred at room temperature for 1 h. The solvent was  
 20 removed under reduced pressure to give the acid chloride quantitatively as a viscous residue, which was used as such for the coupling reaction.

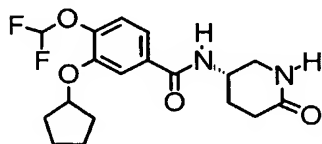
Step 3: Coupling reaction: The acid chloride (step 2) dissolved in dry dichloromethane (5 ml) was added to a well stirred and cooled (0 °C) solution of  
 25 the crude amine (step 1) and triethylamine (137 mg, 1.35 mmol) in dry dichloromethane (5 ml). The mixture was further stirred at room temperature for 1 h. The mixture was diluted with dichloromethane (100 ml) and washed with water (3 x 100 ml), brine (100 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). The crude product obtained after evaporation of the solvent was purified by silica gel column  
 30 chromatography using 3-4 % methanol in chloroform as eluent to give 50 mg of the product as white solid, mp 161-163 °C; IR (KBr) 3307, 2955, 1630, 1504, 1328, 1261, 1224, 1132, 1022, 760 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.55-1.63 (m, 2 H), 1.75-2.14 (m, 8 H), 2.52 (t, *J* = 6.9 Hz, 2 H), 3.24-3.30 (m, 1 H),

3.64-3.70 (m, 1 H), 3.87 (s, 3 H), 4.43-4.54 (m, 1 H), 4.83 (h,  $J = 3.6$  Hz, 1 H), 5.98 (brs, 1 H), 6.24 (brs, 1 H), 6.84 (d,  $J = 8.7$  Hz, 1 H), 7.21 (d,  $J = 8.4$  Hz, 1 H), 7.38 (s, 1 H).

**Example - 53**

(3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-6-oxohexahydropyridine

5



Step 1: (3*S*)-3-Amino-6-oxohexahydropyridine hydrochloride was prepared by the deprotection of (3*S*)-3-(*N*-BOC-Amino)-6-oxohexahydropyridine (215 mg, 1.0 mmol) using 15 % HCl in EtOAc (10 ml) at RT for 3 h.

10

Step 2: 3-Cyclopentyloxy-4-difluoromethoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-difluoromethoxybenzoic acid (200 mg, 0.73 mmol) using oxalyl chloride (140 mg, 1.10 mmol) in dry benzene (5 ml) catalysed by DMF at RT for 1 h.

15

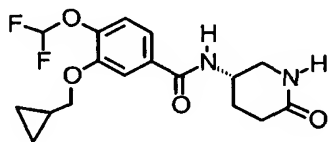
Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (150 mg, 1.48 mmol) in dry dichloromethane (10 ml). The crude product was purified by silica gel column chromatography using 1-2 % methanol in chloroform as eluent to give 180 mg of the product as white solid, mp 58-62 °C; IR (KBr) 3283, 2958, 1655, 1543, 1500, 1268, 1205, 1116, 1048, 993, 761 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.62-2.13 (m, 10 H), 2.49 (t, *J* = 6.9 Hz, 2 H), 3.25-3.30 (m, 1 H), 3.62-3.69 (m, 1 H), 4.42-4.48 (m, 1 H), 4.82-4.91 (m, 1 H), 6.27 (brs, 1 H), 6.57 (t, *J* = 76.2 Hz, 1 H), 6.60 (brs, 1 H), 7.12 (d, *J* = 8.1 Hz, 1 H), 7.21 (d, *J* = 8.1 Hz, 1 H), 7.49 (s, 1 H).

20  
25

**Example - 54**

(3*S*)-3-(3-Cyclopropylmethyloxy-4-difluoromethoxyphenylcarboxamido)-6-oxo-hexahydropyridine

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Step 1: (3*S*)-3-Amino-6-oxohexahydropyridine hydrochloride was prepared by the deprotection of (3*S*)-3-(*N*-BOC-Amino)-6-oxohexahydropyridine (214 mg, 1.0 mmol) using 15 % HCl in EtOAc (10 ml) at RT for 3 h.

10

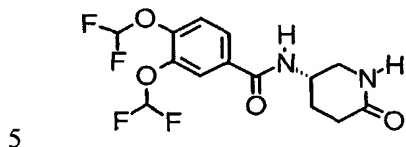
Step 2: 3-Cyclopropylmethyloxy-4-difluoromethoxybenzoyl chloride was prepared from 3-Cyclopropylmethyloxy-4-difluoromethoxybenzoic acid (200 mg, 0.77 mmol) using oxalyl chloride (148 mg, 1.16 mmol) in dry benzene (5 ml) catalysed by DMF at RT for 1 h.

15

Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (150 mg, 1.48 mmol) in dry dichloromethane (5 ml). The crude product was purified by silica gel column chromatography using 3-5 % methanol in chloroform to give 150 mg of the product as a white solid, mp 161-163 °C; IR (KBr) 3282, 1641, 1549, 1507, 1407, 1331, 1271, 1217, 1129, 1055 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.38 (dd, *J* = 5.7, 4.8 Hz, 2 H), 0.69 (dd, *J* = 6.9, 6.3 Hz, 2 H), 1.28-1.35 (m, 1 H), 2.00-2.19 (m, 2 H), 2.55 (t, *J* = 6.9 Hz, 2 H), 3.27-3.33 (m, 1 H), 3.68-3.75 (m, 1 H), 3.95 (d, *J* = 6.9 Hz, 2 H), 4.47-4.52 (m, 1 H), 5.84 (brs, 1 H), 6.30 (brs, 1 H), 6.70 (t, *J* = 75.0 Hz, 1 H), 7.17-7.25 (m, 3 H), 7.47 (s, 1 H).

20

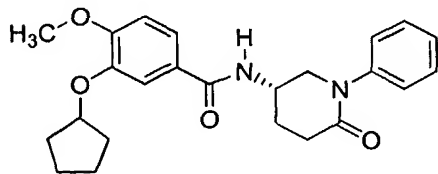
25

**Example - 55**(3*S*)-3-[3,4-Di(di fluoromethoxy)phenylcarboxamido]-6-oxohexahydropyridine

Step 1: (3*S*)-3-Amino-6-oxohexahydropyridine hydrochloride was prepared by the deprotection of (3*S*)-3-(*N*-BOC-Amino)-6-oxohexahydropyridine (214 mg, 1.0 mmol) using 15 % HCl in EtOAc (10 ml) at RT for 3 h.

Step 2: 3,4-Di(di fluoromethoxy)benzoyl chloride was prepared from 3,4-Di(di fluoromethoxy)-benzoic acid (200 mg, 0.78 mmol) using oxalyl chloride (150 mg, 1.18 mmol) in dry benzene (5 ml) catalysed by DMF at RT for 1 h.

Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (180 mg, 1.78 mmol) in dry dichloromethane (5 ml). The crude product was purified by silica gel column chromatography using 3-4 % methanol in chloroform to give 100 mg of the product as white solid, mp 109-114 °C; IR (KBr) 3287, 2955, 1651, 1548, 1504, 1381, 1271, 1201, 1123, 1049, 815, 760 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.00-2.15 (m, 2 H), 2.46-2.52 (m, 2 H), 3.26-3.32 (m, 1 H), 3.32-3.38 (m, 1 H), 4.47-4.57 (m, 1 H), 6.11 (brs, 1 H), 6.56 (t, *J* = 72.6 Hz, 2 H), 6.85 (brs, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.67 (d, *J* = 8.4 Hz, 1 H), 7.75 (s, 1 H).

**Example - 56**(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-6-oxo-1-phenylhexahydro-pyridine

Step 1: (3*S*)-3-Amino-6-oxo-1-phenylhexahydropyridine hydrochloride was prepared by the deprotection of (3*S*)-3-(*N*-BOC-Amino)-6-oxo-1-phenylhexahydropyridine (250 mg, 0.89 mmol) using 15 % HCl in EtOAc (10 ml) at RT for 3 h.

5

Step 2: 3-Cyclopentyloxy-4-methoxybenzoyl chloride was prepared from 3-Cyclopentyloxy-4-methoxybenzoic acid (250 mg, 1.06 mmol) using oxalyl chloride (202 mg, 1.59 mmol) in dry benzene (5 ml) catalysed by DMF at RT for 1 h.

10

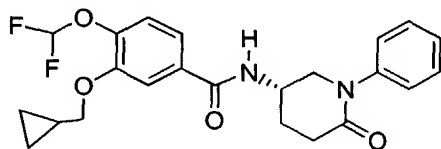
Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (321 mg, 3.17 mmol) in dry dichloromethane (10 ml). The crude product was purified by silica gel column chromatography using 2 % methanol in chloroform as eluent to give 200 mg of the product as white solid, mp 15 165-167 °C; IR (KBr) 3225, 2955, 1664, 1625, 1537, 1330, 1268, 1224, 1023, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.76-2.03 (m, 9 H), 2.24-2.32 (m, 1 H), 2.71 (t, *J* = 6.9 Hz, 2 H), 3.62 (dd, *J* = 7.2, 5.1 Hz, 1 H), 3.87 (s, 3 H), 4.01 (dd, *J* = 7.8, 4.5 Hz, 1 H), 4.58-4.65 (m, 1 H), 4.78-4.85 (m, 1 H), 6.21 (d, *J* = 6.9 Hz, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 7.19-7.25 (m, 4 H), 7.33-7.38 (m, 3 H).

20

#### **Example - 57**

(3*S*)-3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenylcarboxamido)-6-oxo-1-phenyl-hexahydropyridine

25



Step 1: (3*S*)-3-Amino-6-oxo-1-phenylhexahydropyridine hydrochloride was prepared by the deprotection of (3*S*)-3-(*N*-BOC-Amino)-6-oxo-1-phenylhexahydropyridine (100 mg, 0.35 mmol) using 15 % HCl in EtOAc (5 ml) at RT for 3 h.

30

Step 2: 3-Cyclopropylmethyloxy-4-difluoromethoxybenzoyl chloride was prepared from 3-Cyclopropylmethyloxy-4-difluoromethoxybenzoic acid (100 mg, 0.38 mmol) using oxalyl chloride (74 mg, 0.58 mmol) in dry benzene (5 ml) catalysed by DMF at RT for 1 h.

5

Step 3: Coupling reaction: The amine (step 1) was coupled with acid chloride (step 2) using triethylamine (120 mg, 1.19 mmol) in dry dichloromethane (5 ml). The crude product was purified by silica gel column chromatography using 1-2 % methanol in chloroform to give 60 mg of the product as white solid, mp 55-60 °C;

10 IR (KBr) 3314, 2926, 1637, 1593, 1503, 1407, 1272, 1120, 1120, 1024  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.33-3.36 (m, 2 H), 0.62-0.69 (m, 2 H), 1.24-1.31 (m, 1 H), 2.00-2.10 (m, 1 H), 2.24-2.30 (m, 1 H), 2.70 (t,  $J = 6.9$  Hz, 2 H), 3.62 (dd,  $J = 6.9$ , 1.8 Hz, 1 H), 3.91 (d,  $J = 6.9$  Hz, 2 H), 3.98 (dd,  $J = 8.4$ , 3.9 Hz, 1 H), 4.55-4.70 (m, 1 H), 6.40 (brs, 1 H), 6.80 (t,  $J = 75$  Hz, 1 H), 7.13-7.24 (m, 5 H),  
15 7.32-7.37 (m, 2 H), 7.43 (s, 1 H).

### *In vitro* studies

#### Inhibition of Phosphodiesterase enzymes (PDE4)

In this assay, PDE4 enzyme converts [ $^3\text{H}$ ] cAMP to the corresponding [ $^3\text{H}$ ] 5'-AMP in proportion to the amount of PDE4 present. The [ $^3\text{H}$ ] 5'-AMP then was  
20 quantitatively converted to free [ $^3\text{H}$ ] adenosine and phosphate by the action of snake venom 5'-nucleotidase. Hence, the amount of [ $^3\text{H}$ ] adenosine liberated is proportional to PDE4 activity.

The assay was performed at 34°C. in a 200  $\mu\text{l}$  total reaction mixture. The  
25 reaction mixture contained 12.5mM of Tris, 5 mM  $\text{MgCl}_2$ , 1 $\mu\text{M}$  cAMP (cold) and  $^3\text{H}$  cAMP (0.1 $\mu\text{Ci}$ ). Stock solutions of the compounds to be investigated were prepared in DMSO in concentrations such that the DMSO content in the test samples did not exceed 0.05 % by volume to avoid affecting the PDE4 activity. Drug samples were then added in the reaction mixture (25  $\mu\text{l}$ /tube). The assay was  
30 initiated by addition of enzyme mix (75  $\mu\text{L}$ ) and the mixture was incubated for 20 minutes at 34°C. Then the reaction was stopped by boiling the tubes for 2 mins at 100°C in a water bath. After cooling on ice for 5 minutes and addition of 50  $\mu\text{g}$ /reaction of 5'-nucleotidase snake venom from *Crotalus atrox* incubation was

carried out again for 20 min. at 34°C. The unreacted substrate was separated from (3H) Adenosine by addition of Dowex AG 1X-8 (400 ul) which was pre-equilibrated (1:1:1) in water and ethanol. Reaction mixture was then thoroughly mixed, placed on ice for 15 minutes, vortexed and centrifuged at 14,000 r.p.m. for 2 mins. After centrifugation, a sample of the supernatant was taken and added in 24 well optiplates containing Scintillant (1 ml) and mixed well. The samples in the plates were then determined for radioactivity in a Top Counter and the PDE4 activity was calculated. PDE4 enzyme was present in quantities that yield <30% total hydrolysis of substrate (linear assay conditions).

Additionally, activity of the compounds were tested against other Phosphodiesterase enzymes, namely, PDE1 (Ca.sup.2+/calmodulin-dependent), PDE2 (cGMP-stimulated), PDE3 (cGMP-inhibited), PDE5 (cGMP-specific) and PDE6 (cGMP-specific, photoreceptor).

Results were expressed as percent inhibition ( $IC_{50}$ ) in nM concentrations.

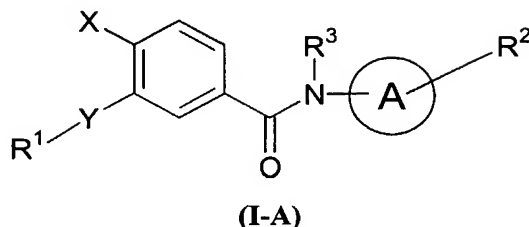
The  $IC_{50}$  values were determined from the concentration curves by nonlinear regression analysis.

Example No.	$IC_{50}$ (in nM)
11	309.0
12	55.45
15	390.0
17	33.84
21	158.9
22	681.4
23	1305.5
25	146.4
26	53.08
31	475.0
32	520.0
33	31.77
34	212.0
35	350.0
53	133.2
54	286.7



**We Claim:**

1 1. A compound of the general formula (I- A)



7 wherein,

8 R<sup>1</sup> is selected from the group consisting of: hydrogen, substituted or unsubstituted  
9 alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,  
10 substituted or unsubstituted cycloalkyl, substituted or unsubstituted  
11 cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or  
12 unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or  
13 unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group,  
14 substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
15 heteroarylalkyl, -C(O)-R<sup>1</sup>, -C(O)O-R<sup>1</sup>, -C(O)NR<sup>1</sup>R<sup>1</sup> and -S(O)<sub>m</sub>-R<sup>1</sup>;

16 Y is selected from the group consisting of direct bond, oxygen, sulfur and NR<sup>1</sup>;

17 X is selected from the group consisting of: hydrogen, halogen atom, -OR<sup>1</sup>, -  
18 S(O)<sub>m</sub>R<sup>1</sup>, -C(O)R<sup>1</sup>, formyl amine, nitro and -NR<sup>x</sup>R<sup>y</sup>;

19 R<sup>x</sup> and R<sup>y</sup> are independently selected from the group consisting of: hydrogen  
20 atom, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted  
21 arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl,  
22 substituted or unsubstituted cycloalkenyl substituted or unsubstituted heterocyclic  
23 ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
24 heteroaryl and substituted or unsubstituted heteroarylalkyl;

25 m is 0, 1 or 2;

26 R<sup>2</sup> is selected from the group consisting of: hydrogen, substituted or unsubstituted  
27 alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl,  
28 substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,  
29 substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted

30 cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted  
 31 arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted  
 32 heterocyclic group, substituted or unsubstituted heterocyclalkyl, substituted or  
 33 unsubstituted heteroarylalkyl, oxo (=O), thio (=S), hydroxy, amino, cyano, nitro,  
 34 halogen, carboxyl and formyl;

35

36 R<sup>3</sup> is selected from the group consisting of: hydrogen, substituted or unsubstituted  
 37 alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl,  
 38 substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,  
 39 substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted  
 40 cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted  
 41 arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted  
 42 heterocyclic group, substituted or unsubstituted heterocyclalkyl, substituted or  
 43 unsubstituted heteroarylalkyl and hydroxy;

44 ring A is a heterocyclic ring wherein R<sup>2</sup> is chosen independently for each position  
 45 capable of substitution,

46 and their analogs, their tautomers, their regioisomers, their diastereomers, their  
 47 stereoisomers, their geometrical isomers, their N-oxides, their polymorphs, their  
 48 pharmaceutically acceptable salts, and their pharmaceutically acceptable solvates  
 49 thereof.

1 2. A compound according to claim 1 wherein the substituents in the  
 2 'substituted alkyl', 'substituted alkoxy' 'substituted alkenyl' 'substituted  
 3 alkynyl' 'substituted cycloalkyl' substituted cycloalkylalkyl' substituted  
 4 cycloalkenyl' 'substituted arylalkyl' 'substituted aryl' 'substituted heterocyclic  
 5 ring', 'substituted heteroaryl ring,' 'substituted heteroarylalkyl', 'substituted  
 6 heterocyclalkyl ring', 'substituted amino', 'substituted alkoxycarbonyl',  
 7 'substituted cyclic ring' 'substituted alkylcarbonyl', 'substituted  
 8 alkylcarbonyloxy' and 'substituted carboxylic acid' may be the same or different  
 9 which one or more selected from the groups such as hydrogen, hydroxy, halogen,  
 10 carboxyl, cyano, amino, nitro, oxo (=O), thio (=S), or optionally substituted  
 11 groups selected from alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl,  
 12 aryl, heteroaryl, heteroarylalkyl, heterocyclic ring, -COOR<sup>x</sup>, -C(O)R<sup>x</sup>, -C(S)R<sup>x</sup>, -  
 13 C(O)NR<sup>x</sup>R<sup>y</sup>, -C(O)ONR<sup>x</sup>R<sup>y</sup>, -NR<sup>x</sup>CONR<sup>y</sup>R<sup>z</sup>, -N(R<sup>x</sup>)SOR<sup>y</sup>, -N(R<sup>x</sup>)SO<sub>2</sub>R<sup>y</sup>, -(=N-  
 14 N(R<sup>x</sup>)R<sup>y</sup>), -NR<sup>x</sup>C(O)OR<sup>y</sup>, -NR<sup>x</sup>R<sup>y</sup>, -NR<sup>x</sup>C(O)R<sup>y</sup>-, -NR<sup>x</sup>C(S)R<sup>y</sup>-NR<sup>x</sup>C(S)NR<sup>y</sup>R<sup>z</sup>, -

15 SONR<sup>x</sup>R<sup>y</sup>-, -SO<sub>2</sub>NR<sup>x</sup>R<sup>y</sup>-, -OR<sup>x</sup>, -OR<sup>x</sup>C(O)NR<sup>y</sup>R<sup>z</sup>, -OR<sup>x</sup>C(O)OR<sup>y</sup>-, -OC(O)R<sup>x</sup>, -  
 16 OC(O)NR<sup>x</sup>R<sup>y</sup>, -R<sup>x</sup>NR<sup>y</sup>R<sup>z</sup>, -R<sup>x</sup>R<sup>y</sup>R<sup>z</sup>, -R<sup>x</sup>CF<sub>3</sub>, -R<sup>x</sup>NR<sup>y</sup>C(O)R<sup>z</sup>, -R<sup>x</sup>OR<sup>y</sup>, -  
 17 R<sup>x</sup>C(O)OR<sup>y</sup>, -R<sup>x</sup>C(O)NR<sup>y</sup>R<sup>z</sup>, -R<sup>x</sup>C(O)R<sup>x</sup>, -R<sup>x</sup>OC(O)R<sup>y</sup>, -SR<sup>x</sup>, -SOR<sup>x</sup>, -SO<sub>2</sub>R<sup>x</sup> and -  
 18 ONO<sub>2</sub>;

19 R<sup>x</sup>, R<sup>y</sup> and R<sup>z</sup> is each independently selected from the group consisting of:  
 20 hydrogen atom, substituted or unsubstituted alkyl, haloalkyl, substituted or  
 21 unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or  
 22 unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl substituted  
 23 or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl,  
 24 substituted or unsubstituted heteroaryl and substituted or unsubstituted  
 25 heteroarylalkyl.

1 3. The compound according to claim 1 or 2 wherein R<sup>1</sup> is chosen from the  
 2 group consisting of: substituted or unsubstituted alkyl, substituted or  
 3 unsubstituted cycloalkyl and substituted or unsubstituted cycloalkylalkyl.

1 4. The compound according to claims 1-2 or 3 wherein Y is oxygen.

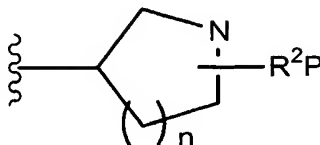
2 5. The compound according to claims 1-3 or 4 wherein X is substituted or  
 3 unsubstituted alkoxy.

1 6. The compound according to claim 1-4 or 5 wherein R<sup>2</sup> is selected from the  
 2 group consisting of: hydrogen, substituted or unsubstituted alkyl, substituted or  
 3 unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted  
 4 arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted  
 5 cycloalkylalkyl, substituted or unsubstituted heteroaryl, substituted or  
 6 unsubstituted heteroarylalkyl, and oxo(=O).

1 7. The compound according to claims 1-5 or 6 wherein R<sup>3</sup> is hydrogen.

1 8. The compound according to claims 1-6 or 7 wherein ring A is

2



3

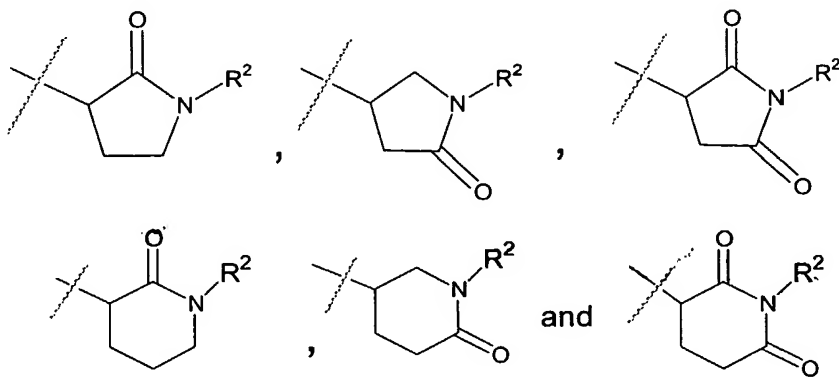
4 wherein  $n = 1$  or  $2$ ;

5  $p = 1, 2, 3, 4$  or  $5$ ; with the proviso that

6 if  $n = 1$  then  $p = 1, 2, 3$  or  $4$ , and

7 if  $n = 2$  then  $p = 1, 2, 3, 4$  or  $5$ .

1 9. The compound according to claim 8 wherein ring A is selected from the  
2 group consisting of:



3

4

1 10. A compound according to claim 1 selected from the group consisting of :

2 (3*S*)-1-[4-(*tert*-Butyl)benzyl]-3-(3-cyclopentyloxy-4-  
3 methoxyphenylcarbox-amido)-2,5-dioxoazolane;

4  
5 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-  
6 cyanobenzyl)-2,5-dioxo-azolane;

7  
8 (3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(3-  
9 trifluoromethyl-benzyl)azolane;

10  
11 (3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(4-  
12 trifluoromethyl-benzyl)azolane;

13

- 14 (3*S*)-1-(3-Bromobenzyl)-3-(3-cyclopentyloxy-4-  
 15 methoxyphenylcarboxamido)-2, 5-dioxo-azolane;  
 16  
 17 (3*R*)-3-(3-Cyclopentyloxy)-4-methoxyphenylcarboxamido)-1-(2, 5-  
 18 dichlorobenzyl)-2, 5-dioxo-azolane;  
 19  
 20 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-  
 21 nitrobenzyl)-2, 5-dioxoazolane;  
 22  
 23 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(4-chloro-3-  
 24 nitrobenzyl)-2, 5-dioxoazolane;  
 25  
 26 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-5-oxoazolane;  
 27  
 28 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,6-  
 29 dioxohexahydropyridine;  
 30  
 31 (3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2,6-  
 32 dioxohexahydropyridine;  
 33  
 34 (3*R*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2,6-  
 35 dioxo-hexahydro-pyridine;  
 36  
 37 (3*S*)-3-(3-Cyclopropylmethyloxy-4-difluoromethoxyphenylcarboxamido)-  
 38 2,6-dioxo-hexahydropyridine;  
 39  
 40 (3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-6-  
 41 oxohexahydropyridine; and  
 42  
 43 (3*S*)-3-(3-Cyclopropylmethyloxy-4-difluoromethoxyphenylcarboxamido)-  
 44 6-oxo-hexahydropyridine.  
 45  
 46  
 1 11. A compound according to claim 1 selected from the group consisting of:  
 2  
 3 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-  
 4 dioxoazolane;  
 5  
 6 (3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-  
 7 dioxoazolane;  
 8  
 9 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-methyl-2,5-  
 10 dioxoazolane;  
 11  
 12 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-  
 13 cyclopropylmethyl-2,5-dioxoazolane;  
 14  
 15 (3*S*)-1-Cyclohexyl-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-  
 16 2,5-dioxoazolane;  
 17

- 18 (3*S*)-1-Cyanomethyl-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-  
 19 2,5-dioxoazolane ;  
 20  
 21 Methyl 2-[(3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-  
 22 dioxoazolan-1-yl]acetate;  
 23  
 24 2-[(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-  
 25 dioxoazolan-1-yl]acetic acid;  
 26  
 27 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-  
 28 phenylazolane;  
 29  
 30 (3*S*)-1-Benzyl-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-  
 31 dioxoazolane;  
 32  
 33 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(3-  
 34 trifluoromethylbenzyl)-azolane;  
 35  
 36 (3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(3-  
 37 trifluoromethylbenzyl)-azolane;  
 38  
 39 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(4-  
 40 trifluoromethylbenzyl)-azolane;  
 41  
 42 (3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,5-dioxo-1-(3-  
 43 trifluoromethylbenzyl)-azolane;  
 44  
 45 (3*R*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-  
 46 cyanobenzyl)-2, 5-dioxoazolane;  
 47  
 48 Ethyl 4-[(3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2, 5-  
 49 dioxoazolan-1-yl]benzoate;  
 50  
 51 Ethyl 3-[(3*S*)-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2, 5-  
 52 dioxoazolan-1-ylmethyl] benzoate;  
 53  
 54 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-  
 55 fluorobenzyl)-2, 5-dioxoazolane; and  
 56  
 57 (3*S*)-3-(3-Cyclopentyloxy)-4-methoxyphenylcarboxamido)-1-(2, 5-  
 58 dichlorophenyl)-2, 5-dioxo-azolane.

- 59  
 1 12. A compound according to claim 1 selected from the group consisting of:  
 2  
 3 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(2, 6-  
 4 dichlorobenzyl)-2, 5-dioxoazolane;  
 5  
 6 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-  
 7 pyridylmethyl)-2, 5-dioxoazolane ;  
 8

- 9 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(3-  
10 oxopyridylmethyl)-2, 5-dioxo-azolane;  
11  
12 (3*S*)-1-Benzyl-3-(3-cyclopentyloxy-4-methoxyphenylcarboxamido)-2-  
13 oxoazolane;  
14  
15 (3*S*)-1-Benzyl-3-(3-cyclopentyloxy-4-  
16 difluoromethoxyphenylcarboxamido)-2-oxoazolane;  
17  
18 (3*S*)-3-(4-Difluoromethoxy-3-methoxyphenylcarboxamido)-2,6-  
19 dioxohexahydro-pyridine;  
20  
21 (3*S*)-3-[3,4-Di(difluoromethoxy)phenylcarboxamido]-2,6-  
22 dioxohexahydropyridine;  
23  
24 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-ethyl-2,6-  
25 dioxohexahydro-pyridine;  
26  
27 Ethyl-2-[(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,6-  
28 dioxo-hexahydro-1-pyridinyl]acetate;  
29  
30 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-1-(2,6-  
31 dichlorobenzyl)-2,6-dioxohexahydropyridine;  
32  
33 (3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-1-(2,6-  
34 dichloro-benzyl)-2,6-dioxohexahydropyridine;  
35  
36 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2,6-dioxo-1-(4-  
37 pyridyl-methyl)-hexahydropyridine;  
38  
39 (3*S*)-3-[3,4-Di(difluoromethoxyphenylcarboxamido)]-1-(4-pyridylmethyl)-  
40 2,6-dioxo-hexahydropyridine;  
41  
42 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2-  
43 oxohexahydropyridine;  
44  
45 (3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2-  
46 oxohexahydro-pyridine;  
47  
48 (3*S*)-3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenylcarboxamido)-2-  
49 oxo-hexahydropyridine;  
50  
51 (3*S*)-3-[3,4-di(difluoromethoxy)phenylcarboxamido]-2-  
52 oxohexahydropyridine;  
53  
54 (3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-2-oxo-1-  
55 phenylhexahydro-pyridine;  
56  
57 (3*S*)-3-(3-Cyclopentyloxy-4-difluoromethoxyphenylcarboxamido)-2-oxo-  
58 1-phenyl-hexahydropyridine;

(3*S*)-3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenylcarboxamido)-2-oxo-1-phenyl-hexahydropyridine;

(3*S*)-3-[3,4-di(difluoromethoxy)phenylcarboxamido]-2-oxo-1-phenylhexahydropyridine;

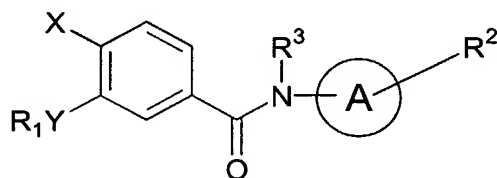
(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-6-oxohexahydropyridine;

(3*S*)-3-[3,4-Di(difluoromethoxy)phenylcarboxamido]-6-oxohexahydropyridine;

(3*S*)-3-(3-Cyclopentyloxy-4-methoxyphenylcarboxamido)-6-oxo-1-phenylhexahydro-pyridine; and

(3*S*)-3-(3-Cyclopropylmethoxy-4-methoxyphenylcarboxamido)-6-oxo-1-phenyl-hexahydropyridine.

13. A process for the preparation of compounds of the general formula (I -A)



(I-A)

wherein,

R<sup>1</sup> is selected from the group consisting of: hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl, -C(O)-R<sup>1</sup>, -C(O)O-R<sup>1</sup>, -C(O)NR<sup>1</sup>R<sup>1</sup> and -S(O)<sub>m</sub>-R<sup>1</sup>;

Y is selected from the group consisting of: direct bond, oxygen, sulfur and NR<sup>1</sup>;

X is selected from the group consisting of: hydrogen, halogen atom, -OR<sup>1</sup>, -S(O)<sub>m</sub> R<sup>1</sup>, -C(O)R<sup>1</sup>, formyl amine, nitro and -NR<sup>x</sup>R<sup>y</sup>, wherein R<sup>x</sup> and R<sup>y</sup> are independently selected from the group consisting of: hydrogen atom, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted arylalkyl, substituted



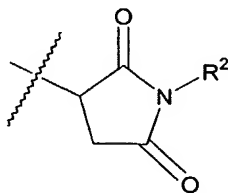
21 or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or  
22 unsubstituted cycloalkenyl substituted or unsubstituted heterocyclic ring,  
23 substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
24 heteroaryl and substituted or unsubstituted heteroarylalkyl;

25 m is 0, 1 or 2;

26  $R^2$  is independently selected for each position capable of substitution from the  
27 group consisting of: hydrogen, substituted or unsubstituted alkyl, substituted or  
28 unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or  
29 unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or  
30 unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl,  
31 substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl,  
32 substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic  
33 group, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
34 heteroarylalkyl, oxo (=O), thio (=S), hydroxy, amino, cyano, nitro, halogen,  
35 carboxyl and formyl;

36 wherein  $R^3$  is selected from the group consisting of: hydrogen, substituted or  
37 unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or  
38 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or  
39 unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted  
40 or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or  
41 unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or  
42 unsubstituted heterocyclic group, substituted or unsubstituted heterocyclalkyl,  
43 substituted or unsubstituted heteroarylalkyl and hydroxy;

44 ring A is



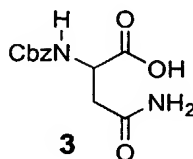
45  
46 and their analogs, their tautomers, their regioisomers, their diastereomers, their  
47 stereoisomers, their geometrical isomers, their N-oxides, their polymorph, their  
48 pharmaceutically acceptable salts, and their pharmaceutically acceptable solvates  
49 thereof;

50

51 comprising the steps of:

52

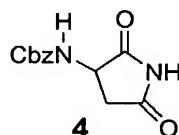
53 (a) Cyclisation of the compound of the formula (3)



54

55

56 with a coupling agent chosen from the group consisting of DCC and HOBT in the  
57 presence of an activator chosen from the group consisting of N-  
58 hydroxysuccinimide and HOBT to yield compounds of the formula (4)

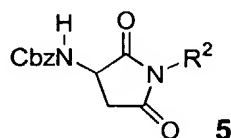


59

60

61 (b) Selective alkylation of the compound of the general formula (4) with alkyl  
62 halides of formula  $R^2X$  to yield the compound of the general formula (5) where  $R^2$   
63 is as previously described

64

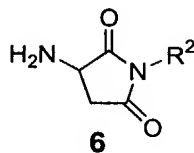


65

66

67 (c) Deprotection of the Cbz group of compound of formula (5) using palladium on  
68 carbon to yield the compound of the general formula (6)

69

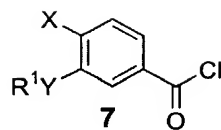


70

71

72 (d) Condensation of the compound of the general formula (6) with compound of  
73 formula (7) where X, Y and  $R^1$  are as previously described

74

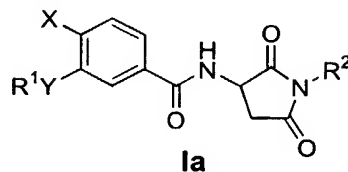


75

76

77 to yield a compound of the general formula **(Ia)**

78

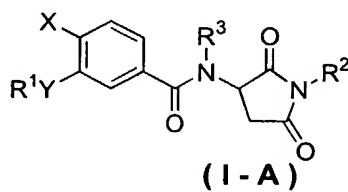


79

80 and

81 (e) reacting the compound of the general formula **(Ia)** with an alkyl halide of the82 formula  $R^3X$  to yield compounds of the general formula **(I)** where is as previously

83 described

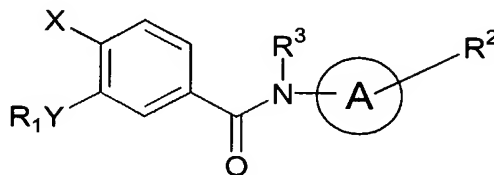


84

85

1 14. A process for the preparation of compounds of the general formula (I-A)

2



3

4

5

(I-A)

6

wherein,

7 R<sup>1</sup> is selected from the group consisting of: hydrogen, substituted or unsubstituted  
8 alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,  
9 substituted or unsubstituted cycloalkyl, substituted or unsubstituted  
10 cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or  
11 unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or  
12 unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group,  
13 substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
14 heteroarylalkyl, -C(O)-R<sup>1</sup>, -C(O)O-R<sup>1</sup>, -C(O)NR<sup>1</sup>R<sup>1</sup> and -S(O)<sub>m</sub>-R<sup>1</sup>

15 Y is selected from the group consisting of: direct bond, oxygen, sulfur and NR<sup>1</sup>

16 X is selected from the group consisting of: hydrogen, halogen atom, -OR<sup>1</sup>, -  
17 S(O)<sub>m</sub>R<sup>1</sup>, -C(O)R<sup>1</sup>, formyl amine, nitro and -NR<sup>x</sup>R<sup>y</sup>

18 R<sup>x</sup> and R<sup>y</sup> are independently selected from the group consisting of: hydrogen  
19 atom, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted  
20 arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl,  
21 substituted or unsubstituted cycloalkenyl substituted or unsubstituted heterocyclic  
22 ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
23 heteroaryl and substituted or unsubstituted heteroarylalkyl

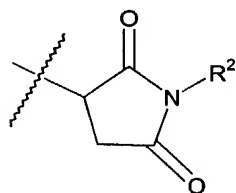
24 m is 0, 1 or 2;

25 R<sup>2</sup> is selected from the group consisting of: hydrogen, substituted or unsubstituted  
26 alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl,  
27 substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,  
28 substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted  
29 cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted  
30 arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted

heterocyclic group, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, oxo (=O), thio (=S), hydroxy, amino, cyano, nitro, halogen, carboxyl, and formyl

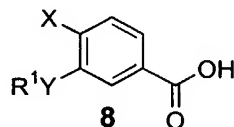
R<sup>3</sup> is selected from the group consisting of: hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl and hydroxy

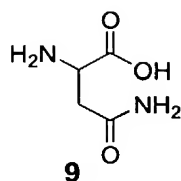
ring A is



and their analogs, their tautomers, their regiosomers, their diastereomers, their stereoisomers, their geometrical isomers, their N-oxides, their polymorphs, their pharmaceutically acceptable salts and their pharmaceutically acceptable solvents thereof comprising the steps of:

(a) Coupling of compound of the general formula (8) with compound of formula (9)



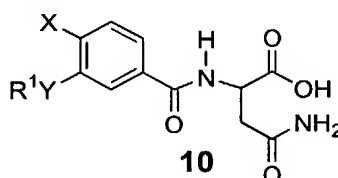


55

56

57 in the presence of a coupling agent chosen from the group consisting of DCC and  
 58 EDCA optionally in the presence of an activator chosen from the group consisting  
 59 of HOBT and N-hydroxysuccinimide to yield a compound of the general formula  
 60 **(10)**

61

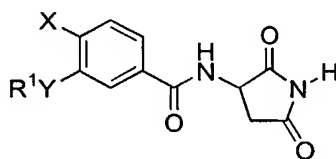


62

63

64 **(b)** Cyclisation of the compound of the general formula **(10)** in the presence of  
 65 DCC in DMF to yield a compound of the general formula **(11)** where X, Y and R<sup>1</sup>  
 66 is as previously described.

67

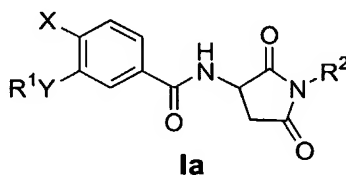


68

69

70 **(c)** Reaction of compound of formula **(11)** with alkyl halides of general formula  
 71 R<sup>2</sup>X gives the compound of formula **(Ia)** where R<sup>2</sup> is as previously described

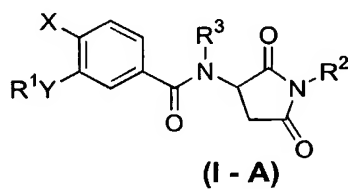
72



73

74

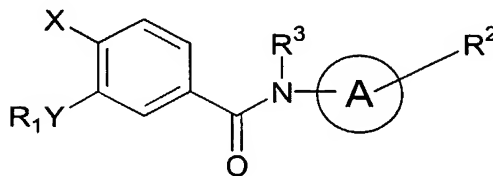
75 (d) reacting the compound of the formula (Ia) with an alkyl halide of the  
76 formula  $R^3X$  to get the novel compounds of the formula (I-A) where  $R^3$  is as  
77 previously described



78

1 15. A process for the preparation of compounds of the general formula (I-A)

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6

(I-A)

7 wherein,

8 R<sup>1</sup> selected from the group consisting of: hydrogen, substituted or unsubstituted  
9 alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,  
10 substituted or unsubstituted cycloalkyl, substituted or unsubstituted  
11 cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or  
12 unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or  
13 unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group,  
14 substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
15 heteroarylalkyl, -C(O)-R<sup>1</sup>, -C(O)O-R<sup>1</sup>, -C(O)NR<sup>1</sup>R<sup>1</sup> and -S(O)<sub>m</sub>-R<sup>1</sup>

16 Y is selected from the group consisting of: direct bond, oxygen, sulfur and NR<sup>1</sup>

17 X is selected from the group consisting of: a hydrogen, halogen atom, -OR<sup>1</sup>, -  
18 S(O)<sub>m</sub> R<sup>1</sup>, -C(O)R<sup>1</sup>, formyl amine, nitro and -NR<sup>x</sup>R<sup>y</sup> R<sup>x</sup> and R<sup>y</sup> are independently  
19 selected from the group consisting of: hydrogen atom, substituted or  
20 unsubstituted alkyl, haloalkyl, substituted or unsubstituted arylalkyl, substituted or  
21 unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or  
22 unsubstituted cycloalkenyl substituted or unsubstituted heterocyclic ring,  
23 substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
24 heteroaryl and substituted or unsubstituted heteroarylalkyl;

25 m is 0, 1 or 2;

26 wherein R<sup>2</sup> is selected from the group consisting of: hydrogen, substituted or  
27 unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or  
28 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or  
29 unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted  
30 or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or  
31 unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or

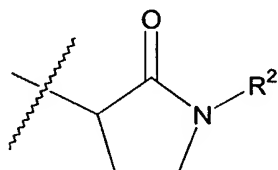


32 unsubstituted heterocyclic group, substituted or unsubstituted heterocyclalkyl,  
 33 substituted or unsubstituted heteroarylalkyl, oxo (=O), thio (=S), hydroxy, amino,  
 34 cyano, nitro, halogen, carboxyl, and formyl

35

36 wherein  $R^3$  is selected from the group consisting of: hydrogen, substituted or  
 37 unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or  
 38 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or  
 39 unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted  
 40 or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or  
 41 unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or  
 42 unsubstituted heterocyclic group, substituted or unsubstituted heterocyclalkyl,  
 43 substituted or unsubstituted heteroarylalkyl and hydroxy

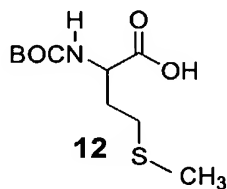
44 wherein ring A is



45

46 and their analogs, their tautomers, their regiosomers, their diastereomers, their  
 47 stereoisomers, their geometrical isomers, their N-oxides, their polymorphs, their  
 48 pharmaceutically acceptable salts and their pharmaceutically acceptable solvents  
 49 thereof comprising the steps of:

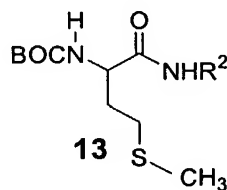
50 (a) Condensation of compound of the formula (12)



51

52

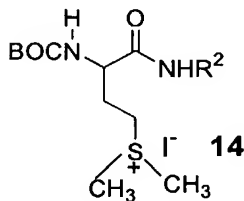
53 with an amine of formula  $R^2NH_2$  to yield a the compound of general formula (13)



54

55

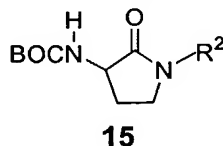
56 (b) Alkylation of the compound of the general formula (13) with methyl iodide to  
 57 yield a compound of the general formula (14) where  $R^2$  is as previously described  
 58



59

60

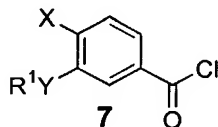
61 (c) Intramolecular cyclisation of the compound of the general formula (14) in the  
 62 presence of a base to yield a compound of the general formula (15)



63

64 (d) Deprotection of the BOC group of compound of formula (15) followed by  
 65 condensation with compound of formula (7) where X, Y, and  $R^1$  are as previously  
 66 described

67

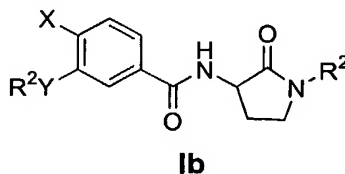


68

69

70 to yield a compound of the general formula (Ib)

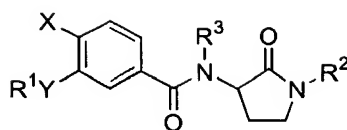
71



72

73

74 (e) reacting the compound of the general formula (Ib) with an alkyl halide of the  
 75 formula  $R^3X$  to yield a compound of the general formula (I) where  $R^3$  is as  
 76 previously described



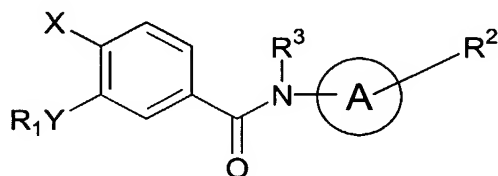
(I-A)

77

78

1 16. A process for the preparation of compounds of the general formula (I-A)

2



(I-A)

3

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5 wherein,

6 R<sup>1</sup> is selected from the group consisting of: hydrogen, substituted or unsubstituted  
 7 alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,  
 8 substituted or unsubstituted cycloalkyl, substituted or unsubstituted  
 9 cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or  
 10 unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or  
 11 unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group,  
 12 substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
 13 heteroarylalkyl, -C(O)-R<sup>1</sup>, -C(O)O-R<sup>1</sup>, -C(O)NR<sup>1</sup>R<sup>1</sup> and -S(O)<sub>m</sub>-R<sup>1</sup>

14 Y is selected from the group consisting of direct bond, oxygen, sulfur or NR<sup>1</sup>;  
 15 preferably Y is oxygen

16 X is selected from the group consisting of: a hydrogen, halogen atom, -OR<sup>1</sup>, -  
 17 S(O)<sub>m</sub> R<sup>1</sup>, -C(O)R<sup>1</sup>, formyl amine, nitro and -NR<sup>x</sup>R<sup>y</sup>

18 R<sup>x</sup> and R<sup>y</sup> are independently selected from the group consisting of: hydrogen  
 19 atom, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted  
 20 arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl,  
 21 substituted or unsubstituted cycloalkenyl substituted or unsubstituted heterocyclic  
 22 ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
 23 heteroaryl and substituted or unsubstituted heteroarylalkyl

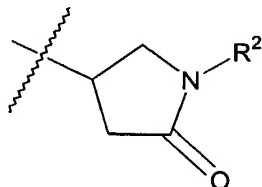
24 m is 0, 1 or 2;

25 wherein  $R^2$  is selected from the group consisting of: hydrogen, substituted or  
 26 unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or  
 27 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or  
 28 unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted  
 29 or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or  
 30 unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or  
 31 unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl,  
 32 substituted or unsubstituted heteroarylalkyl, oxo (=O), thio (=S), hydroxy, amino,  
 33 cyano, nitro, halogen, carboxyl, and formyl

34

35 wherein  $R^3$  is selected from the group consisting of: hydrogen, substituted or  
 36 unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or  
 37 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or  
 38 unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted  
 39 or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or  
 40 unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or  
 41 unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl,  
 42 substituted or unsubstituted heteroarylalkyl and hydroxy

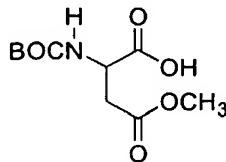
43 ring A is



44  
45

46 and their analogs, their tautomers, their regiosomers, their diastereomers, their  
 47 stereoisomers, their geometrical isomers, their N-oxides, their polymorphs, their  
 48 pharmaceutically acceptable salts and their pharmaceutically acceptable solvents  
 49 thereof comprising the steps of:

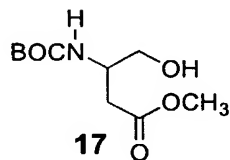
50 (a) Reduction of a compound of the formula (16) via its mixed anhydride



51

52 (16)

53 in the presence of NaBH<sub>4</sub> to yield the compounds of the formula (17)

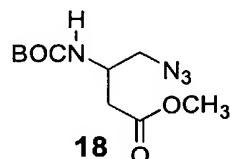


54

55

56 (b) Mesylation of compound of formula 17 followed by treatment with sodium  
57 azide to yield a compound of the formula (18).

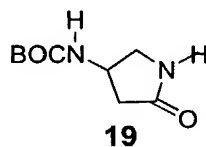
58



59

60

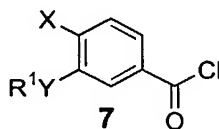
61 (c) Palladium catalysed reductive cyclisation of compound of formula (18) to  
62 yield a compound of the formula (19).



63

64 (d) Deprotection of compound of formula (19) followed by condensation with  
65 compound of formula (7) where X, Y, R<sup>1</sup> and R<sup>2</sup> are as previously described

66

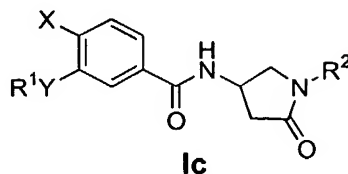


67

68

69 to yield a compound of formula (Ic)

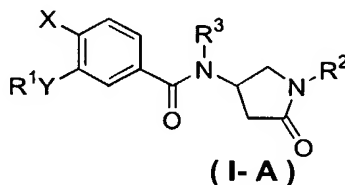
70



71

72

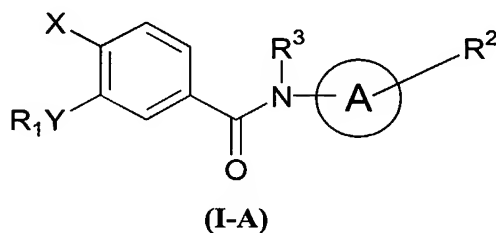
73 (e) reacting the compound of the formula (Ic) with an alkyl halide of the formula  
 74  $R^3X$  to get the novel compounds of the formula (I-A) where is as described  
 75 previously



76

1 17. A process for the preparation of compounds of the general formula (I-A)

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5 wherein,

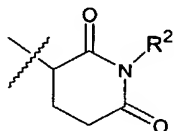
6  $R^1$  is selected from the group consisting of: hydrogen, substituted or unsubstituted  
 7 alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,  
 8 substituted or unsubstituted cycloalkyl, substituted or unsubstituted  
 9 cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or  
 10 unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or  
 11 unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group,  
 12 substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
 13 heteroarylalkyl,  $-C(O)-R^1$ ,  $-C(O)O-R^1$ ,  $-C(O)NR^1R^1$  and  $-S(O)_m-R^1$   
 14 Y is selected from the group consisting of direct bond, oxygen, sulfur and  $NR^1$   
 15 X is selected from the group consisting of: a hydrogen, halogen atom,  $-OR^1$ , -  
 16  $S(O)_m R^1$ ,  $-C(O)R^1$ , formyl amine, nitro and  $-NR^xR^y$ ;  
 17  $R^x$  and  $R^y$  are independently selected from the group consisting of: hydrogen  
 18 atom, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted  
 19 arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl,  
 20 substituted or unsubstituted cycloalkenyl substituted or unsubstituted heterocyclic  
 21 ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
 22 heteroaryl and substituted or unsubstituted heteroarylalkyl  
 23 m is 0, 1 or 2;

24 R<sup>2</sup> is selected from the group consisting of: hydrogen, substituted or unsubstituted  
 25 alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl,  
 26 substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,  
 27 substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted  
 28 cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted  
 29 arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted  
 30 heterocyclic group, substituted or unsubstituted heterocyclalkyl, substituted or  
 31 unsubstituted heteroarylalkyl, oxo (=O), thio (=S), hydroxy, amino, cyano, nitro,  
 32 halogen, carboxyl, and formyl

33

34 R<sup>3</sup> is selected from the group consisting of: hydrogen, substituted or unsubstituted  
 35 alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl,  
 36 substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,  
 37 substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted  
 38 cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted  
 39 arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted  
 40 heterocyclic group, substituted or unsubstituted heterocyclalkyl, substituted or  
 41 unsubstituted heteroarylalkyl and hydroxy

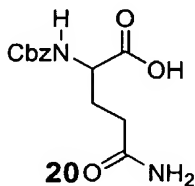
42 ring A is



43

44 and their analogs, their tautomers, their regiosomers, their diastereomers, their  
 45 stereoisomers, their geometrical isomers, their N-oxides, their polymorphs, their  
 46 pharmaceutically acceptable salts and their pharmaceutically acceptable solvents  
 47 thereof comprising the steps of:

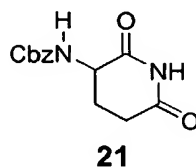
48 (a) Cyclisation of the compound of general formula (20)



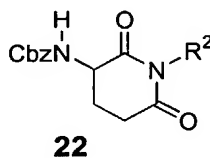
49

50

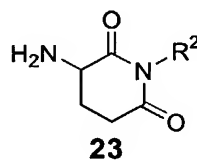
51 with DCC in the presence of N-hydroxysuccinimide in DMF to yield compounds  
52 of the formula (21)



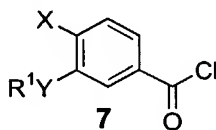
54  
55  
56 (b) Alkylation of the compound of general formula (21) with alkyl halides of  
57 formula  $R^2X$  to yield the compound of the general formula (22) where  $R^2$  is as  
58 previously described



60  
61  
62 (c) Deprotection of the Cbz group of compound of formula (5) using palladium on  
63 carbon in the presence of hydrogen or a hydrogen source to yield a compound of  
64 formula (23)

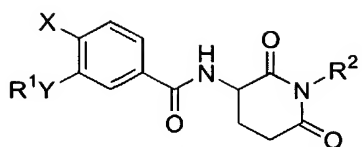


66  
67 (d) Condensation of the compound of the general formula (23) with compound of  
68 formula (7)



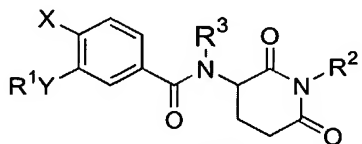
70  
71  
72 yield a compound of the general formula (Id)





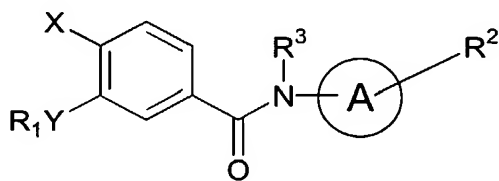
**Id**

(e) reacting the compound of the formula (Ia) with alkyl halide of the formula  $R^3X$  to yield a compound of the general formula (I-A) is as previously described



**(I-A)**

18. A process for the preparation of compounds of the general formula (I-A)



**(I-A)**

$R^1$  is selected from the group consisting of: hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl,  $-C(O)-R^1$ ,  $-C(O)O-R^1$ ,  $-C(O)NR^1R^1$  and  $-S(O)_m-R^1$

Y is selected from the group consisting of: direct bond, oxygen, sulfur and  $NR^1$

X is selected from the group consisting of: a hydrogen, halogen atom,  $-OR^1$ ,  $-S(O)_m R^1$ ,  $-C(O)R^1$ , formyl amine, nitro and  $-NR^xR^y$ ;

$R^x$  and  $R^y$  are independently selected from the group consisting of: represents hydrogen atom, substituted or unsubstituted alkyl, haloalkyl, substituted or

19 unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or  
20 unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl substituted or  
21 unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl,  
22 substituted or unsubstituted heteroaryl or substituted or unsubstituted  
23 heteroarylalkyl

24 m is 0, 1 or 2;

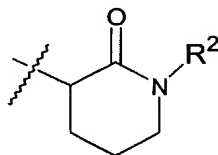
25 wherein  $R^2$  is selected from the group consisting of: hydrogen, substituted or  
26 unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or  
27 unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or  
28 unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted  
29 or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or  
30 unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or  
31 unsubstituted heterocyclic group, substituted or unsubstituted heterocyclalkyl,  
32 substituted or unsubstituted heteroarylalkyl, oxo (=O), thio (=S), hydroxy, amino,  
33 cyano, nitro, halogen, carboxyl, and formyl

34

35  $R^3$  is selected from the group consisting of: hydrogen, substituted or unsubstituted  
36 alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl,  
37 substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,  
38 substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted  
39 cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted  
40 arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted  
41 heterocyclic group, substituted or unsubstituted heterocyclalkyl, substituted or  
42 unsubstituted heteroarylalkyl and hydroxy

43 ring A is

44

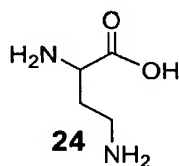


45

46

47 and their analogs, their tautomers, their regiosomers, their diastereomers, their  
48 stereoisomers, their geometrical isomers, their N-oxides, their polymorphs, their  
49 pharmaceutically acceptable salts and their pharmaceutically acceptable solvents  
50 thereof comprising the steps of:

51 (a) Esterification of the compound of general formula (24)

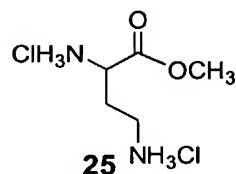


52

53

54 with SOCl<sub>2</sub> in methanol to yield a compound of the formula (25)

55



56

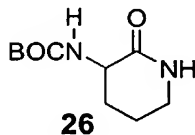
57

58 (b) Intramolecular cyclisation of the compound of the formula (25) in the presence

59 of a base chosen from the group consisting of: triethylamine (TEA) and

60 diisopropylethylamine in the presence of (BOC)<sub>2</sub>O to yield a compound of the

61 formula (26)



62

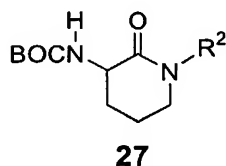
63

64 (c) Alkylation of the compound of general formula (26) with alkyl halides of

65 formula R<sup>2</sup>X to get the compound of the general formula (27) where R<sup>2</sup> is as

66 previously described

67



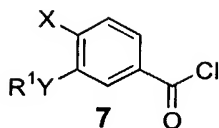
68

69

70 (d) Condensation of the compound of the general formula (27) with compound of

71 formula (7) where X, Y, and R<sup>1</sup> are as previously described

72

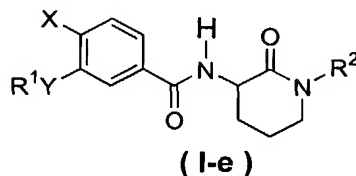


73

74

75 to yield a compound of the general formula (Ie)

76



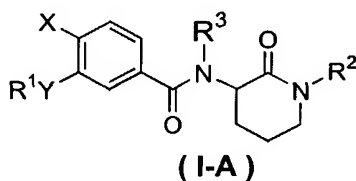
77

78

79 (e) reacting the compound of the formula (I-e) with an alkyl halide of the formula

80 R³X to get the novel compounds of the formula (I-A) where is as previously

81 described

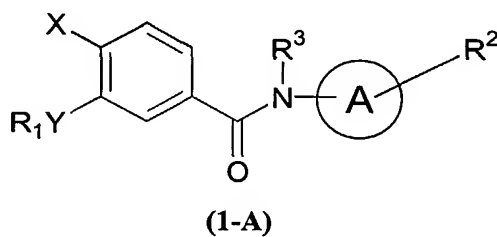


82

83

1 19. A process for the preparation of compounds of the general formula (1)

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5 wherein,

6 R¹ is selected from the group consisting of: hydrogen, substituted or unsubstituted

7 alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,

8 substituted or unsubstituted cycloalkyl, substituted or unsubstituted

9 cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or

10 unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or

11 unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group,

12 substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
13 heteroarylalkyl,  $-C(O)-R^1$ ,  $-C(O)O-R^1$ ,  $-C(O)NR^1R^1$  and  $-S(O)_m-R^1$

14 Y is selected from the group consisting of: direct bond, oxygen, sulfur and  $NR^1$

15 X is selected from the group consisting of: hydrogen, halogen atom,  $-OR^1$ , -  
16  $S(O)_m R^1$ ,  $-C(O)R^1$ , formyl amine, nitro and  $-NR^xR^y$ ;

17  $R^x$  and  $R^y$  are independently represents hydrogen atom, substituted or  
18 unsubstituted alkyl, haloalkyl, substituted or unsubstituted arylalkyl, substituted or  
19 unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or  
20 unsubstituted cycloalkenyl substituted or unsubstituted heterocyclic ring,  
21 substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted  
22 heteroaryl and substituted or unsubstituted heteroarylalkyl

23 m is 0, 1 or 2;

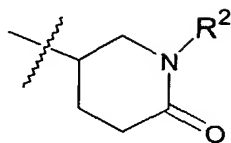
24

25  $R^2$  is selected from the group consisting of: hydrogen, substituted or unsubstituted  
26 alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl,  
27 substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,  
28 substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted  
29 cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted  
30 arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted  
31 heterocyclic group, substituted or unsubstituted heterocyclalkyl, substituted or  
32 unsubstituted heteroarylalkyl, oxo ( $=O$ ), thio ( $=S$ ), hydroxy, amino, cyano, nitro,  
33 halogen, carboxyl, and formyl

34

35  $R^3$  is selected from the group consisting of: hydrogen, substituted or unsubstituted  
36 alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl,  
37 substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl,  
38 substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted  
39 cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted  
40 arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted  
41 heterocyclic group, substituted or unsubstituted heterocyclalkyl, substituted or  
42 unsubstituted heteroarylalkyl and hydroxy

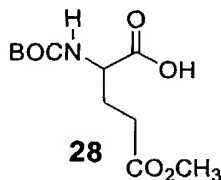
43 wherein ring A is



44

45 and their analogs, their tautomers, their regiosomers, their diastereomers, their  
46 stereoisomers, their geometrical isomers, their N-oxides, their polymorphs, their  
47 pharmaceutically acceptable salts and their pharmaceutically acceptable solvents  
48 thereof comprising the steps of:

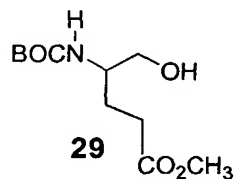
49 (a) Selective reduction of the compound of the formula (28) via its mixed  
50 anhydride



51

52

53 in the presence of NaBH<sub>4</sub> to yield a compound of the formula (29)

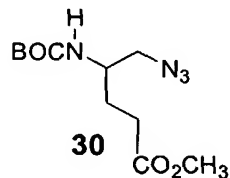


54

55

56 (b) Mesylation of compound of formula (29) followed by treatment with sodium  
57 azide to yield a compound of the formula (30).

58

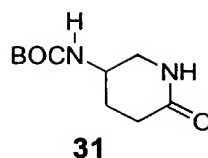


59

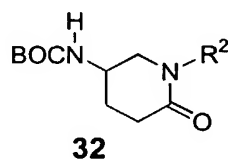
60

61 (c) Palladium catalysed reductive cyclisation of compound of formula (30) to  
62 yield compound of the formula (31).

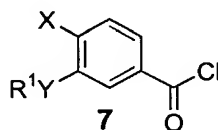
63



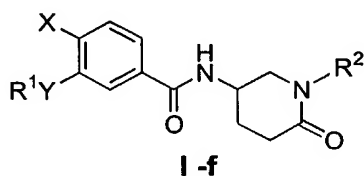
(c) Alkylation of the compound of general formula (31) with alkyl halides of formula  $R^2X$  to yield a compound of the general formula (32) where  $R^2$  is as previously described



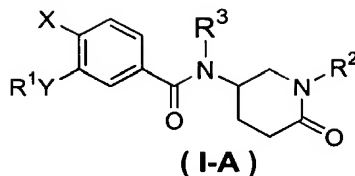
(d) Acylation of compound of the general formula (32) with compound of formula (7) where X, Y, and  $R^1$  are as previously described



to yield a compound of the general formula (I-f) where X, Y,  $R^1$  and  $R^2$  are the same as described above



(e) reacting the compound of the general formula (I-f) with an alkyl halide of the formula  $R^3X$  to get the novel compounds of the formula (I-A) where is as previously described



85

86

- 1    **20.**    A pharmaceutical composition comprising a compound according to
- 2                    claims 1-11 or 12 and pharmaceutically acceptable salts or solvates thereof
- 3                    as well as pharmaceutically acceptable diluents or carriers.
- 4
- 1    **21.**    A method of treating inflammatory diseases, disorders and conditions
- 2                    characterized by or associated with an undesirable inflammatory immune
- 3                    response and all disease and conditions induced by or associated with an
- 4                    excessive secretion of TNF- $\alpha$  and PDE-4 which comprises administering
- 5                    to a subject in need thereof a therapeutically effective amount of a
- 6                    compound according to claims 1-11 or 12.
- 1    **22.**    A method of treating inflammatory conditions and immune disorders in a
- 2                    subject in need thereof which comprises administering to said subject a
- 3                    therapeutically effective amount of a compound according to claim 1.
- 1    **23.**    The method according to claim 22 wherein said inflammatory conditions
- 2                    immune disorders is chosen from the group consisting of: asthma, chronic
- 3                    obstructive pulmonary disease, allergic rhinitis, eosinophilic granuloma,
- 4                    nephritis, rheumatoid arthritis, cystic fibrosis, chronic bronchitis, multiple
- 5                    sclerosis, Crohns disease, psoriasis, urticaria, adult vernal conjunctivitis,
- 6                    respiratory distress syndrome, rheumatoid spondylitis, osteoarthritis, gouty
- 7                    arthritis, utelitis, allergic conjunctivitis, inflammatory bowel conditions,
- 8                    ulcerative colitis, eczema, atopic dermatitis and chronic inflammation.
- 1    **24.**    The method according to claim 22 wherein said inflammatory conditions
- 2                    and immune disorders are selected from the group consisting of:
- 3                    inflammatory conditions or immune disorders of the lungs, joints, eyes,
- 4                    bowels, skin and heart.



- 1   **25.**   The method according to claim 23 wherein said inflammatory condition is  
2           chosen from the group consisting of: bronchial asthma, nepritis, and  
3           allergic rhinitis.  
4
- 1   **26.**   A method for abating inflammation in an affected organ or tissue  
2           comprising delivering to said organ or tissue a therapeutically effective  
3           amount of a compound according to claims 1-11 or 12.  
4
- 1   **27.**   A method of treating diseases of the central nervous system in a subject in  
2           need thereof which comprises administering to said subject a  
3           therapeutically effective amount of a compound according to claims 1-11  
4           or 12.  
5
- 1   **28.**   The method according to claim 27 wherein said diseases of the central  
2           nervous system are chosen from the group consisting of: depression,  
3           amnesia, dementia, Alzheimers disease, cardiac failure, shock and  
4           cerebrovascular disease.
- 29.**   A method of treating insulin resistant diabetes in a subject in need thereof  
          which comprises administering to said subject a therapeutically effective  
          amount of a compound according to claims 1-11 or 12.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 03/03721

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D207/40 C07D401/06 C07D207/38 C07D211/88 C07D211/76  
 C07K5/06 A61K31/4015 A61K31/45 A61K31/454 A61P11/06  
 A61P25/28 A61P29/00 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 47545 A (WANNAMAKER MARION W; BEMIS GUY W (US); MURCKO MARK A (US); VERTEX) 23 September 1999 (1999-09-23) page 109, compounds 32b, 32c, 32e claims 1,3,16,18-20,23,24 ---	1-29
X,Y	D. J. FOX ET AL: "Design, Synthesis, and Preliminary Pharmacological Evaluation of N-Acyl-3-aminoglutaramides as Broad-Spectrum Chemokine Inhibitors in Vitro and Anti-inflammatory Agents in Vivo" JOURNAL OF MEDICINAL CHEMISTRY, vol. 45, no. 2, 2002, pages 360-370, XP002267550 page 360, abstract; page 363, table 2; page 363, scheme 1, compound 11 page 368, line 15 - line 32 --- -/--	1-29



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance  
 "E" earlier document but published on or after the international filing date  
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 "O" document referring to an oral disclosure, use, exhibition or other means  
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  
 "&" document member of the same patent family

Date of the actual completion of the international search

21 January 2004

Date of mailing of the international search report

04/02/2004

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Hass, C

## INTERNATIONAL SEARCH REPORT

In ☐ International Application No

PCT/IB 03/03721

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 041 861 A (ORGANON LABOR LTD) 7 September 1966 (1966-09-07) claims 1,4,5; example VI ---	1-9, 20, 27, 28
X	WO 92 10476 A (SEARLE & CO) 25 June 1992 (1992-06-25) claims 1-5, 39; examples 45, 46 ---	1-8, 20, 27, 28
X	EP 0 497 564 A (RHONE POULENC RORER LTD) 5 August 1992 (1992-08-05) page 2, line 32 -page 4, line 12; claims 1, 10, 11 ---	1-7, 20-28
X	WO 94 20446 A (CELLTECH LTD) 15 September 1994 (1994-09-15) claims 1, 21; example 4A page 2, line 6 - line 19 page 12, line 5 -page 13, line 4 ---	1-7, 20-26
X	WO 95 20578 A (PALFREYMAN MALCOLM NORMAN; RHONE POULENC RORER LTD (GB); THURAIRAT) 3 August 1995 (1995-08-03) claims 1, 10-13, 20, 21, 23-31 ---	1-5, 7, 20-29
X	WO 94 02465 A (MORLEY ANDREW DAVID; PALFREYMAN MALCOLM NORMAN (GB); RHONE POULENC) 3 February 1994 (1994-02-03) claims 1-9, 20-24, 28, 34, 35, 37, 42-50 ---	1, 2, 5, 7, 20-29
X	WO 95 01338 A (BYK GULDEN LOMBERG CHEM FAB; AMSCHLER HERMANN (DE)) 12 January 1995 (1995-01-12) page 14, line 1 -page 17, line 3 page 19, line 18 -page 20, line 13 claims 1, 22-25 & US 5 712 298 A 27 January 1998 (1998-01-27) cited in the application ---	1-5, 7, 20-26
X	WO 01 70746 A (MATSUMOTO TATSUMI; TARUI NAOKI (JP); FUJII NOBUHIRO (JP); KAWANO Y) 27 September 2001 (2001-09-27) page 527, compound 153; page 528, compounds 168, 169, 173, 174; page 540, compounds 478, 479, 480; page 541, compounds 563, 564; page 545, compound 554; abstract -& EP 1 270 577 A 2 January 2003 (2003-01-02) ---	1, 2, 6, 7, 20-26, 29
P, X		

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 03/03721

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 04046 A (RHONE-POULENC RORER LTD; MORLEY ANDREW DAVID (GB); PALFREYMAN MALC) 9 February 1995 (1995-02-09) cited in the application claims 1,22,41-49 ---	1,2,5,7, 20-28
X	WO 01 70673 A (DU PONT PHARM CO) 27 September 2001 (2001-09-27) page 232 -page 239 page 240, line 28 -page 241, line 35; claims 1,8-12 ---	1,2,5,7, 20-26
X	DE 20 59 358 A (MERCK & CO INC) 9 June 1971 (1971-06-09) page 12, line 4 - line 31; claims 1,22; example 10 ---	1,2,6,7, 20-24,26
X	WO 01 27107 A (SQUIBB BRISTOL MYERS CO; AHMAD SALEEM (US); ATWAL KARNAIL S (US);) 19 April 2001 (2001-04-19) page 196, sixth row of compounds claims 1,31 ---	1,2,5,7, 20
X	PATENT ABSTRACTS OF JAPAN vol. 011, no. 398 (C-466), 25 December 1987 (1987-12-25) & JP 62 158253 A (KIRIN BREWERY CO LTD), 14 July 1987 (1987-07-14) abstract -----	1-4,7

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-7, 20-29 (all partly)

Present claims 1-7 as well as claims 20-29, as far as they dependent of claims 1-7, relate to an extremely large number of possible compounds, products and methods. Support within the meaning of Article 6 PCT and concrete disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds, products and methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported by all of the examples and actually disclosed in the description, namely those parts relating to the compounds of claims 8-12, process claims 13-29 (which refer to these compounds), and claims 20-29, directed to pharmaceutical compositions and methods, as far as they refer to compounds of claims 8-12.

Moreover, claim 1 is unclear with regard to the term "substituted" which is used without further definition. For the purpose of search, the term "substituted" in claim 1 was considered as to be defined according to present claim 2 so that the search has been restricted to those definitions.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

national application No.  
PCT/IB 03/03721**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 21-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-7, 20-29 (all partly)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Int l Application No

PCT/IB 03/03721

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9947545	A	23-09-1999	AU 3098699 A	11-10-1999
			BG 104863 A	30-04-2001
			BR 9909660 A	21-11-2000
			CA 2324226 A1	23-09-1999
			CN 1323314 T	21-11-2001
			EP 1064298 A2	03-01-2001
			HU 0103575 A2	28-02-2002
			ID 27002 A	22-02-2001
			JP 2002506878 T	05-03-2002
			NO 20004546 A	09-11-2000
			NZ 506963 A	31-10-2003
			PL 343611 A1	27-08-2001
			SK 13822000 A3	09-04-2001
			TR 200103406 T2	21-06-2002
			WO 9947545 A2	23-09-1999
			US 2003232986 A1	18-12-2003
			US 6531474 B1	11-03-2003
			ZA 200004652 A	05-02-2002
GB 1041861	A	07-09-1966	NONE	
WO 9210476	A	25-06-1992	US 5202344 A	13-04-1993
			AT 116638 T	15-01-1995
			AU 9057191 A	08-07-1992
			CA 2097517 A1	12-06-1992
			DE 69106532 D1	16-02-1995
			DE 69106532 T2	08-06-1995
			DK 561941 T3	06-03-1995
			EP 0561941 A1	29-09-1993
			ES 2067322 T3	16-03-1995
			IE 914293 A1	17-06-1992
			JP 6503827 T	28-04-1994
			PT 99739 A	30-11-1992
			WO 9210476 A1	25-06-1992
			US 5314886 A	24-05-1994
EP 0497564	A	05-08-1992	AT 132134 T	15-01-1996
			AT 165334 T	15-05-1998
			AU 664694 B2	30-11-1995
			AU 1188192 A	27-08-1992
			AU 4565196 A	02-05-1996
			CA 2101423 A1	29-07-1992
			CZ 9301528 A3	13-04-1994
			DE 69207017 D1	08-02-1996
			DE 69207017 T2	05-09-1996
			DE 69225245 D1	28-05-1998
			DK 497564 T3	29-01-1996
			EP 0497564 A1	05-08-1992
			EP 0569414 A1	18-11-1993
			EP 0669311 A1	30-08-1995
			ES 2081563 T3	01-03-1996
			FI 933357 A	19-08-1993
			WO 9212961 A1	06-08-1992
			GR 3018544 T3	31-03-1996
			HU 64942 A2	28-03-1994
			HU 9500720 A3	28-12-1995
			IE 920247 A1	29-07-1992
			IL 100788 A	10-01-1997

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

PCT/IB 03/03721

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0497564	A		JP 2664538 B2	15-10-1997
			JP 6504782 T	02-06-1994
			MX 9200344 A1	01-03-1993
			NO 932701 A	21-09-1993
			NZ 241427 A	26-08-1994
			PL 169994 B1	30-09-1996
			SK 80993 A3	08-12-1993
			US 5935978 A	10-08-1999
			US 6255326 B1	03-07-2001
			US 5698711 A	16-12-1997
			ZA 9200547 A	03-05-1993
WO 9420446	A	15-09-1994	AT 207051 T	15-11-2001
			AU 675511 B2	06-02-1997
			AU 6148994 A	26-09-1994
			CA 2135480 A1	15-09-1994
			DE 69428650 D1	22-11-2001
			DE 69428650 T2	01-08-2002
			DK 640065 T3	12-11-2001
			EP 0640065 A1	01-03-1995
			ES 2162623 T3	01-01-2002
			WO 9420446 A1	15-09-1994
			JP 8505158 T	04-06-1996
			NZ 262170 A	24-02-1997
			PT 640065 T	29-04-2002
			SI 640065 T1	30-06-2002
			US 5962483 A	05-10-1999
			US 5739144 A	14-04-1998
WO 9520578	A	03-08-1995	AT 164575 T	15-04-1998
			AU 1463195 A	15-08-1995
			DE 69501947 D1	07-05-1998
			DE 69501947 T2	27-08-1998
			EP 0741707 A1	13-11-1996
			WO 9520578 A1	03-08-1995
			JP 9509654 T	30-09-1997
			ZA 9500639 A	26-07-1996
WO 9402465	A	03-02-1994	AU 4717693 A	14-02-1994
			CA 2140441 A1	03-02-1994
			CZ 9500147 A3	17-07-1996
			EP 0652868 A1	17-05-1995
			FI 950375 A	27-01-1995
			WO 9402465 A1	03-02-1994
			HU 72656 A2	28-05-1996
			HU 211979 B3	29-01-1996
			JP 8503925 T	30-04-1996
			MX 9304571 A1	31-05-1994
			NO 950319 A	27-03-1995
			NZ 254881 A	25-09-1996
			PL 307265 A1	15-05-1995
			US 5935978 A	10-08-1999
			US 5679696 A	21-10-1997
			US 6255326 B1	03-07-2001
			US 5698711 A	16-12-1997
			ZA 9305448 A	19-05-1994
			US 5840724 A	24-11-1998



## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 03/03721

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9501338	A	12-01-1995	AT 217612 T	15-06-2002
			AU 687087 B2	19-02-1998
			AU 7490794 A	24-01-1995
			CA 2165192 A1	12-01-1995
			CN 1126468 A ,B	10-07-1996
			CZ 9600001 A3	12-06-1996
			DE 59410119 D1	20-06-2002
			DK 706513 T3	09-09-2002
			WO 9501338 A1	12-01-1995
			EP 0706513 A1	17-04-1996
			ES 2176252 T3	01-12-2002
			FI 956333 A	29-12-1995
			HK 1011690 A1	11-10-2002
			HU 73232 A2	29-07-1996
			JP 8512041 T	17-12-1996
			JP 3093271 B2	03-10-2000
			NO 955211 A	21-12-1995
			NZ 271316 A	24-11-1997
			PL 311820 A1	18-03-1996
			PT 706513 T	31-10-2002
			RU 2137754 C1	20-09-1999
			SI 706513 T1	31-10-2002
			SK 161795 A3	03-07-1996
			US 5712298 A	27-01-1998
WO 0170746	A	27-09-2001	AU 3955001 A	03-10-2001
			CA 2404226 A1	27-09-2001
			EP 1270577 A1	02-01-2003
			WO 0170746 A1	27-09-2001
			JP 2001335579 A	04-12-2001
WO 9504046	A	09-02-1995	WO 9504046 A1	09-02-1995
WO 0170673	A	27-09-2001	AU 5084901 A	03-10-2001
			BR 0109467 A	03-06-2003
			CA 2401870 A1	27-09-2001
			CZ 20023033 A3	15-01-2003
			EP 1263755 A2	11-12-2002
			HU 0300850 A2	28-07-2003
			JP 2003528072 T	24-09-2003
			SK 13072002 A3	05-08-2003
			WO 0170673 A2	27-09-2001
			US 2002016336 A1	07-02-2002
DE 2059358	A	09-06-1971	CA 945991 A1	23-04-1974
			CH 577475 A5	15-07-1976
			DE 2059358 A1	09-06-1971
			FR 2081325 A5	03-12-1971
			GB 1289187 A	13-09-1972
			JP 49039267 B	24-10-1974
			NL 7016899 A	07-06-1971
			US 3846553 A	05-11-1974
WO 0127107	A	19-04-2001	AU 7859600 A	23-04-2001
			BR 0014725 A	17-06-2003
			CA 2388813 A1	19-04-2001
			EP 1224183 A2	24-07-2002
			HU 0300195 A2	28-07-2003

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 03/03721

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0127107	A	JP 2003527331 T	16-09-2003
		NO 20021717 A	10-06-2002
		TR 200201014 T2	21-01-2003
		WO 0127107 A2	19-04-2001
<hr/>			
JP 62158253	A	14-07-1987	NONE
<hr/>			